DOCTORAL THESIS

Oral Corticosteroids as an Alternative Treatment for Acute Otitis Media in Children

Ranakusuma, Respati Wulansari

Award date:
2020

Oral Corticosteroids as an Alternative Treatment for Acute Otitis Media in Children

Respati Wulansari Ranakusuma

Submitted in total fulfilment of the requirements of the degree of

Doctor of Philosophy (PhD)

September 2019

Faculty of Health Sciences and Medicine

Professor Christopher Del Mar, FAFPHM, MBBChir, MA, MD, FRACGP, BSc

Associate Professor Elaine Beller, BSc, MAppStat

Dr. Amanda McCullough, PhD, PGCHET, BSc (Hons)

This research was supported by an Australian Government Research Training Program Scholarship

ABSTRACT

Background – Antibiotic resistance is a well-recognised global health problem which is mostly driven by antibiotic use that is not evidence based. Acute otitis media (AOM), an acute middle ear inflammation mostly found in children, has a high antibiotic prescribing rate, although only one third of AOM cases (severe AOM) will benefit from antibiotics. Therefore, an effective non-antibiotic treatment for AOM is needed. To date, studies on these alternatives (e.g., decongestants, probiotics) for AOM have demonstrated insufficient evidence of efficacy. Due to the inflammatory nature of AOM, an anti-inflammatory agent, such as corticosteroids, could be a potential candidate. Although corticosteroids have been used for inflammatory and autoimmune diseases, their efficacy in AOM remains unknown.

Aim – To assess the effectiveness of systemic corticosteroids as a monotherapy for mild AOM and as an addition to antibiotics for severe AOM.

Methods – We conducted four studies. The first study was a Cochrane systematic review where we identified, appraised, and synthesised available randomised clinical trials (RCTs) of systemic corticosteroids versus placebo for AOM in children. Our second study was a feasibility study surveying Indonesian physicians to understand their current management of children with AOM and their willingness to participate in our planned RCT. Following the feasibility survey study, we conducted our third study, a pilot pragmatic, randomised, single-blind, controlled study. This pilot study also included a mechanistic sub-study using tympanometry. The study tested the feasibility of all pre-specified procedures and measures of the planned large trial, as well as assessing the effects of oral corticosteroids in improving the middle ear effusion (MEE) in AOM and the correlation between ear pain and other symptom resolution and MEE. Our last study was the finalisation of the protocol for the full-sized RCT based on the results from the pilot study.

Results – Our first study, a Cochrane review, demonstrated insufficient evidence for both efficacy and harm for corticosteroids in AOM thus justifying our decision to design a large, high-quality RCT.

To inform the design of the RCT, we conducted our second study, a feasibility survey study. This confirmed it was feasible to conduct the main RCT in Indonesia by identifying there were sufficient numbers of paediatric AOM cases and physicians who would be willing to: (1)

withhold antibiotics and choose observation for mild AOM; (2) prescribe corticosteroids; and (3) participate in our RCT.

Our third study, a pilot study (62 children were recruited, 60 were analysed), demonstrated that it was feasible to successfully implement all pre-specified procedures and measures, and verified we needed fewer children for the main RCT than initially envisaged. We found oral corticosteroids may potentially reduce pain intensity measured using a 100-mm Visual Analogue Scale at Day 3 (mean difference [*MD*] -7.37, 95% CI -13.36 to -1.39, *P* = 0.017), but cause more drowsiness than placebo (relative risk [*RR*] 1.77, 95% CI 1.11 to 2.81, *P* = 0.016; number needed to harm (NNTH) 3). No excess of other adverse events (e.g., nausea, vomiting, diarrhea) was attributed to oral corticosteroid use and there were no serious adverse events. Oral corticosteroids may also improve tympanometry curves at Day 7 (*RR* 1.76, 95% CI 1.04 to 2.97; *P* = 0.047; number needed to treat to benefit (NNTB) 3), but with only a small correlation between pain and other AOM-relevant symptoms and MEE.

The findings and feedback from these studies helped us to improve and finalise our fourth study, which is the protocol for a full-scale pragmatic, parallel, randomised double-blind, placebo-controlled study.

Conclusions – Our Cochrane review demonstrated there was insufficient evidence about the effects of systemic corticosteroids for AOM and therefore, the need for a large high-quality RCT. Our feasibility survey and pilot study also confirmed it was feasible and important to conduct a pragmatic, parallel, randomised, double-blind, placebo-controlled study, to be able to provide definitive conclusions about the effectiveness and harm of oral corticosteroids for children with AOM. If this study demonstrates positive results, physicians would be able to withhold antibiotics and prescribe oral corticosteroids as a monotherapy for mild AOM and prescribe corticosteroids in addition to antibiotics for severe AOM. Long term or second-line antibiotics would not be required. The consequent reduction in antibiotic use would lead to fewer adverse events and reduced antibiotic resistance.

Keywords

Drug resistance, bacterial; Anti-bacterial agents; Otitis media; Acute disease; Child; Therapeutics; Glucocorticoids; Systematic review; Survey and questionnaires; Health services; Primary health care; Hospitals; Pilot projects; Visual Analogue Scale; Acoustic impedance tests; Pragmatic clinical trial; Randomized controlled trial; Treatment failure; Drug-related side effects and adverse reactions.

DECLARATION BY AUTHOR

This thesis is submitted to Bond University in fulfilment of the requirements of the degree of Doctor of Philosophy by Research.

This thesis represents my own original work towards this research degree and contains no material that has previously been submitted for a degree or diploma at this University or any other institution, except where due acknowledgement is made.

Name : Respati Wulansari Ranakusuma

Date : 27 September 2019

Signature :

DECLARATION BY CO-AUTHORS

Respati W Ranakusuma (RR) is the author of Chapter 1 (General Introduction) and Chapter 6 (Conclusions and Implications). Four chapters which include publications (four published, one submitted for publication), are multi-authored on which RR was the lead. RR was responsible for the design, conception, planning, and preparation; data collection, management, analysis, and interpretation; initial drafting, submission for publication, response to reviewers, and subsequent revisions of publication, of all five papers from four studies.

Roles of the co-authors were providing substantial feedback particularly in the study design, methods, planning, and conduct of Study 3, which was a clinical trial. They also provided assistance with data analysis and interpretation, as well as substantial revision of the manuscript.

Publications co-authored	Statement of contribution
Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews.* 2016;7:CD012289 [published protocol]	RR 62%, YP 5%, EDS 5%, ST 5%, EMB 10%, SS 3%, CDM 10%
Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews*. 2018;3:CD012289 [published review]	RR 65%, YP 4%, EDS 4%, ST 5%, EMB 10%, SS 2%, CDM 10%
Ranakusuma RW, McCullough AR, Beller EM, Del Mar CB, Safitri ED, Pitoyo Y, Widyaningsih. Current management of children with acute otitis media: a feasibility survey for a pragmatic study. *Paediatrica Indonesiana.* 2019;59(6):303-7.	RR 60%, ARM 10%, EMB 10%, CDM 10%, EDS 3%, YP 3%, WN 4%

https://doi.org/10.14238/pi59.6.2019.303-17 [published]	
Ranakusuma RW, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, Beller EM. Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study (OPAL study). *Pilot and Feasibility Studies*. 2018;4:146. doi 10.1186/s40814-018-0337-x. [published]	RR 50%, ARM 10%, EDS 5%, YP 5%, WN 5%, CDM 10%, EMB 15%
Ranakusuma RW, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, Beller EM. Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, controlled study (OPAL study). *Pilot and Feasibility Studies.* [submitted for publication – under review].	RR 50%, ARM 10%, EDS 5%, YP 5%, WN 5%, CDM 10%, EMB 15%
Ranakusuma RW, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Beller EM, Del Mar CB. A Protocol for a Pragmatic, Randomised, Double-Blinded, Placebo-Controlled Study of Oral Prednisolone for Acute Otitis Media in Children. [submitted for publication as an appendix of the previous paper]	RR 55%, ARM 5%, EDS 5%, YP 5%, WN 5%, EMB 20%, CDM 5%

RESEARCH OUTPUTS

Peer-reviewed publications

1. **Ranakusuma RW**, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews 2018*, Issue 3. Art. No.: CD012289. https://doi.org/10.1002/14651858.CD012289.pub2 [published].
2. **Ranakusuma RW**, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews 2016*, Issue 7. Art. No.: CD012289. https://doi.org/10.1002/14651858.CD012289 [published].
3. **Ranakusuma RW**, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, Beller EM. Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study (OPAL study). *Pilot and Feasibility Studies*. 2018;4:146. https://doi.org/10.1186/s40814-018-0337-x [published].
4. **Ranakusuma RW**, McCullough AR, Beller EM, Del Mar CB, Safitri ED, Pitoyo Y, Widyaningsih. Current management of children with acute otitis media: a feasibility survey for a pragmatic study. *Paediatrica Indonesiana*. 2019;59(6):303-7. https://doi.org/10.14238/pi59.6.2019.303-17 [published].
5. **Ranakusuma RW,** McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, Beller EM. Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, controlled study (OPAL study) [submitted to *Pilot and Feasibility Studies* – under review].

Peer-reviewed conference abstracts – Oral presentations

1. **Ranakusuma RW**, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Alternative treatment for acute respiratory infections: Systemic corticosteroids for acute otitis media in children – a Cochrane review. Antimicrobials 2017 Conference, 23-25 February 2017, Adelaide Convention Centre, Adelaide, Australia.
2. **Ranakusuma RW**, McCullough A, Beller E, Del Mar C, Sastroasmoro S, Bashiruddin J. The feasibility study of an oral corticosteroid for acute otitis media in children: A pragmatic randomised controlled trial in Indonesia. Higher Degree Research Conference

2016 Faculty of Health Sciences and Medicine Bond University, 12 October 2016, Gold Coast, Australia.

Peer-reviewed conference abstracts – Poster presentations

1. **Ranakusuma RW**, McCullough A, Beller EM, Del Mar C, Bashiruddin J, Sastroasmoro S. How do clinicians treat acute otitis media? A feasibility survey for a clinical trial testing corticosteroids for acute otitis media in children. The 19th International Symposium on Recent Advances in Otitis Media (RAOM) 2017, 4 – 8 June 2017, Gold Coast Convention and Exhibition Centre, Gold Coast, Australia.

Travel grants

1. Otitis Media Australia (OMOZ) 2018, 14-16 August 2018, Darwin Convention Centre, Darwin, Australia [participant].

ETHICS DECLARATION

The research associated with this thesis received ethics approval from the Bond University Human Research Ethics Committee (BUHREC) and the ethics committee of the Faculty of Medicine, Universitas Indonesia.

Our second study of "The current management of children with acute otitis media: a feasibility survey for a pragmatic study in Jakarta, Depok, and Bekasi" received ethics approval from the BUHREC with ethics application number 15756 (17 October 2016). We also received ethics approval from the ethics committee of the Faculty of Medicine, Universitas Indonesia with ethics approval letter No. 320/UN2.F1/ETIK/2016 (25 April 2016).

Our third study of "Oral prednisolone for acute otitis media in children: a pilot pragmatic randomised, open-label, controlled study (OPAL Study)" received ethics approval from the BUHREC with ethics application number 16151 (28 November 2017) with amendment ethics application number 16208 (24 January 2018). We also received ethics approval from the ethics committee of the Faculty of Medicine, Universitas Indonesia with protocol number 17-08-0858 and ethics approval letter No. 852/UN2.F1/ETIK/2017 (11 September 2017) with amendment ethics approval letter No. 1088/UN2.F1/ETIK/X/2017 (23 October 2017).

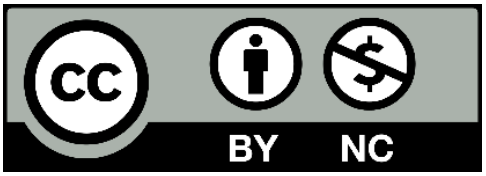
COPYRIGHT DECLARATION

This thesis makes careful note of all sections which have been previously published, along with relevant copyright information.

Publications, which include the protocol and full review, in Chapter 2 (Cochrane review of systemic corticosteroids for acute otitis media in children) are reproduced under the agreement between the author (RR) and the John Wiley & Sons, Inc. RR is granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the full article of these publications for Dissertation/Thesis, print and electronic, with the Licence Number 4612760317753 and 4612760766532 (Licence date 19 June 2019).

The publication in Chapter 3 (Current management of children with acute otitis media: a feasibility survey for a pragmatic study) is reproduced under the Attribution-Non Commercial-Share Alike 4.0 International (CC BY-NC-SA 4.0). This permits the sharing, copying, redistribution, adaptation, remix, and transform upon the material for any purpose. To view a copy of this licence, visit: https://creativecommons.org/licenses/by-nc-sa/4.0/.

The publication in Chapter 4 (Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study or OPAL study) is reproduced under the Attribution 4.0 International Licence (CC BY 4.0). This permits the sharing, copying, redistribution, adaptation, remix, and transform upon the material for any purpose. To view a copy of this licence, visit: http://creativecommons.org/licenses/by-nc/4.0/.



ACKNOWLEDGEMENTS

First and mostly, I would like to thank Allah Subhanahu Wa Ta'ala (SWT) for blessings and guidance. My faith in Allah SWT and the strength Allah SWT granted me has helped me go through the ups and downs in the past four years of my candidature and I am very grateful and blessed.

I would like to thank my primary supervisor, Professor Chris Del Mar for his kindness and time to welcome me and listen to my dream to become a PhD student as part of being a better clinician; for the opportunity and support that he has granted me to pursue my dream by welcoming me into his extraordinary team in the Institute for Evidence-Based Healthcare (IEBH); for every minute he spent providing me with feedback, brilliant ideas, and mental support in numerous meetings and chats; for all the effort to help me throughout my candidature, particularly during my extensive and challenging clinical trial in Jakarta, Indonesia. He is such an inspirational supervisor and teacher. I pray to Allah SWT for his rapid recovery so he will be able to be back to the IEBH soon. I want to thank my secondary supervisor, Associate Professor Elaine Beller for her continuous support during my study, for the time she has spent with me in numerous fruitful discussions and Skype meetings during her retirement. I would like to thank her for not giving up on me and opening my insights and interest in conducting a clinical trial. I cannot be thankful enough for her thoughtfulness, patience, encouragement, and support. I also want to thank my third supervisor, Dr Amanda McCullough, who joined the team later in my candidature for being a wonderful supervisor and friend, and for her encouraging words, support, constructive feedback, her eagle-eyes, and critical comments on my manuscripts.

I would like to thank my OPAL Study team: Vonny for her continuous support, loyalty, hard work, prayers, and patience; Rizki, Dimas, Redha, Ibrena, Rantung, and Fajri for their hard work and I hope this experience will bring new insight in their clinical work; and all the physicians, nurses, audiologists, pharmacists, all my patients and their parents for their participation and commitment.

I would like to thank Professor Paul Glasziou for opening his door and welcoming me to become one of his students at the IEBH and giving me a lifetime and extraordinary experience to learn and work with the most excellent and smart group of people I have ever met. I am also thankful to the following IEBH staff: Chrissy for her assistance and support

since way before I entered my PhD candidature; Melanie for making my study much easier; Rae for her warm, beautiful heart and for every calming and thoughtful chat; Tammy for her unimaginable support and help in assisting me to gain my scholarship; Jenny for the opportunity to involve me as one of tutors in her class; Anna for morning chats and support; Justin for his help with library support and all his jokes; Sharon for inspiring chats and support; Liz for her support while I was doing the Cochrane review; Mark for his help on a statistics; Ray for all the support and warm smiles; Paulina for nice chats and beautiful shoes; and also to everyone in the IEBH: Rebecca, David, Claudia, Magnolia, Clare, Ruwani, Matt, Connor, Iris, Amanda, Kate, and Zoe. I would also like to thank Michael for his support during my clinical trial in using MASCoT.

I would like to thank Julie Jory, Tanya Forbes, Neil Roberts, Treasure McGuire, David Pache, Elizabeth Gordon, Sarah Savage, David Honeyman, and all administration, research, and library staff in the Faculty of Health Sciences and Medicine for their support and help throughout my study. I would also like to acknowledge the financial support I received during my study from the Australian Government Research Training Program Scholarship, the Australian National Health and Medical Research Council (NHMRC) as part of the Centre for Research Excellence in Minimising Antibiotic Resistance for Acute Respiratory Infections (CREMARA), and the Advance Queensland Women's Academic Fund, Australia.

I would like to express my gratitude to people at my workplace in Jakarta, Indonesia, the Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit Dr Cipto Mangunkusumo General Hospital and Faculty of Medicine Universitas Indonesia: Professor Dr Siti Setiati for her support and opportunity she granted me to pursue my dream; Professor Dr Sudigdo Sastroasmoro for his support and love and for introducing me to evidence-based practice and the research world for the very first time; Professor Dr Jenny Bashiruddin for her endless support; Dr Kuntjoro Harimurti and Dr Indah S Widyaningsih for being such inspirational teachers; Dr Tifauzia Tyassuma, Dr CH Soejono, Professor Dr Ratna Sitompul, Dr Lies Dina Liastuti, Dr Ratna D. Restuti, Professor Dr Ari Fahrial Syam, Dr Nina Kemala Sari, Dr Andri Lubis, Dr Sukamto, Rana, Fitriani, and other CEEBM staff, as well as the Research and Human Resource staff at Dr Cipto Mangunkusumo General Hospital.

To my supportive friends in Australia, I would to thank: Shreas for being my true friend who was always there for me and for all those free 'consultations', Oyuka for becoming my first

true friend when I was starting my PhD, Gina for all her support and chats, Mina for his encouragement, smile and funny jokes during my down moments, Warda for the beautiful friendship, Alex for quick afternoon chat and snacks, and Loai and Eman for their support, kindness, and delicious food. Our friendships have helped me go through the ups and downs during my candidature with the laughs, cakes, grain waves, chocolates, KFC, hugs, and joy. I hope our friendships will be long-lasting! To my long-time friends in Jakarta: Handa whose strength has been encouraging and inspirational; Upit, Eka, Riris, and Ade for their support and prayers; Vanda, Zihar, Ritchie, Ninda, and Sasha for the beautiful friendship and I cannot be thankful enough for their support to me and to each other; and Yuli, Duma, and my ENT friends for their love and support. I would love to thank all of them for the beautiful and sincere friendship. Time and place have met me with them, and I am so grateful to call them my lifetime best friends.

Finally, I would like to express my greatest gratitude to my parents; My father and mother, Teguh and Elly Ranakusuma for all the life and love they have given me, all timeless support and effort, non-stop prayers, and to continuously believe in me and make me believe myself in getting through all the obstacles. I cannot stop thanking Allah SWT for sending them as my parents and making me the luckiest daughter in the world. I hope I have made you proud. I would also like to thank my sisters and brothers: Legia, Octaviani, Emil, Reino, Satrio, and Olivia for their sincere prayers, endless love, and moral and emotional support; my nieces and nephew: Rafa, Kayla, Kirana, Sarita, Pasha, and Kyra for all fun times and support; and my cousins: Mita and Isti for beautiful sisterhood and fun chats.

With the support of these beautiful persons above, I have the spirit, motivation, and strength to get through four years of my PhD journey with confidence and a smile on my face. So, thank you!

Respati W Ranakusuma (Anggi)

REFLECTION OF MY PHD JOURNEY

My PhD journey started in February 2016, when I commenced my Master of Science by Research at Centre for Research in Evidence-Based Practice (CREBP), currently known as the Institute for Evidence-Based Healthcare (IEBH), Bond University. I was then transmuted as a PhD candidate in January 2017.

My original idea for a PhD was driven by my main concern about antibiotic resistance in Indonesia. As an ENT specialist, I have encountered wide use of antibiotics for self-limiting diseases such ARIs, which were self-initiated by patients or prescribed by other physicians. This irrational practice can lead to an increased risk of antibiotic resistance. One of the common ARIs with high antibiotic prescribing is AOM. As a physician, I find diagnosing and treating AOM challenging. I observed that most physicians would prescribe antibiotics for AOM patients due to potential complications, such as perforation of the tympanic membrane. Although I sometimes prescribe oral corticosteroids as a monotherapy or as an addition to antibiotics for AOM patients, I found this practice was not recommended by any international practice guidelines but was practiced by other ENT specialists. My concern and personal experience assisted me to develop my PhD research topic in alternative non-antibiotic treatments as part of the comprehensive management of AOM in children. Therefore, I was encouraged to investigate the role of oral corticosteroids for AOM, as the anti-inflammatory nature of corticosteroids would theoretically cover the pathogenesis of AOM, which is the inflammation of the middle ear. This initial research question led me to develop a research flowchart (see Figure 1).

The development of my research question, which led to other studies in order to respond to my initial question has taken me on an extraordinary journey during my PhD candidature. It has provided many opportunities to improve my skill and knowledge, as well as enhance my experience as a student, researcher, and teacher during my PhD candidature.

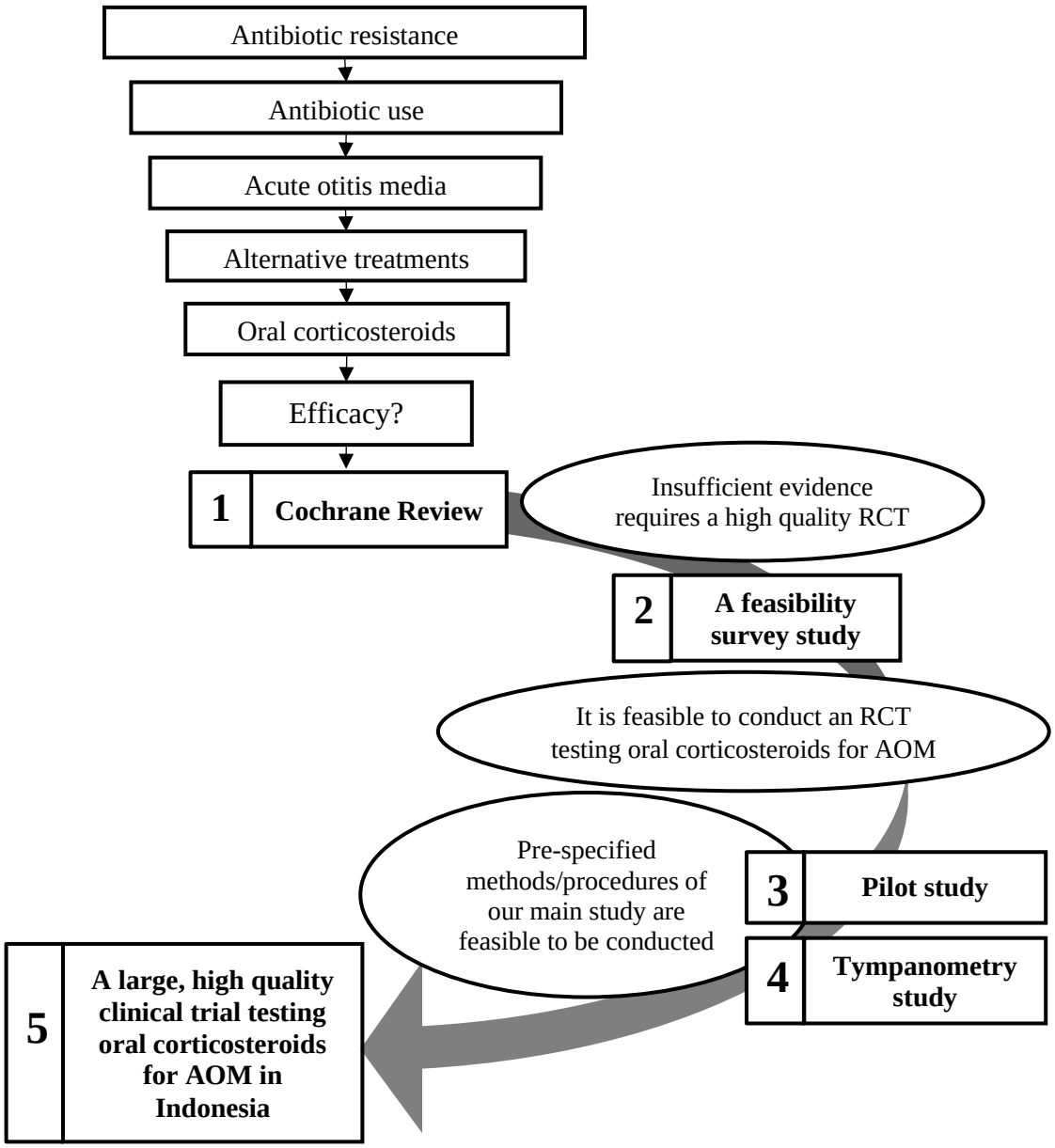


Figure 1. Research flowchart

My journey as a student

I am so fortunate that I am studying at the best research centre in Australia and the world, the IEBH Bond University. The IEBH has provided me with many opportunities to improve my competency as a physician, researcher, and teacher in evidence-based practice (EBP), as well as other research fields through workshops (e.g., EBP, systematic reviews (SR), publication skills) and other several internal scientific sessions for staff and students, such as journal club and skill sessions. I found these sessions were very helpful. The journal club sessions have built my knowledge and skill in identifying and critically appraising published studies, and then summarising and interpreting the results for their applicability to clinical practice by

investigating limitations and strengths. I had the opportunity to attend mandatory classes and guest lectures as well as casual lectures provided by Bond University that are relevant to my study and research in general. I also had the opportunity to work as a research assistant for several projects at the IEBH, which enabled me to work in a team that required the ability to multitask under a prespecified timeline and become critical and more communicative.

My journey as a researcher

As a researcher, I learned to work according to a pre-planned timeline which made me better organised and critical, able to work under pressure and think 'outside the box' and be a better decision-maker. I also learned to be a manager of all my studies where I had to lead and work with other personnel in the team who had different personal education backgrounds and characteristics. I am extremely fortunate that my supervisors have fully supported me throughout the process by sharing their valuable expertise and experience in conducting clinical trials and applying for research grants. They were also very helpful in supporting me to think systematically in planning and problem solving. I found the whole process in resolving my research questions was systematically well-planned and each process has been complementary and supportive to each other in an appropriate sequence.

During my studies, I found many challenges, as well as benefits. One challenge I found was maintaining good collaboration with participating personnel from different backgrounds of professional education and personal characteristics. This has improved my skill in developing and maintaining a trustable, communicative relationship and respectful collaboration with all research personnel (e.g., participating healthcare personnel, the directors or the head of healthcare institutions and departments, research assistants and co-investigators) and study participants and their parents. I personally feel responsible for introducing and disseminating the importance of research as part of the improvement of the quality of healthcare service. Therefore, I tried to place myself as a clinician who is eager to improve the quality of practice by implementing a well-conducted clinical trial to resolve the gap between the evidence and clinical practice. I expect this could be a good example for other physicians and young researchers and be able to encourage them to become involved in clinical research.

Overall, the whole process has built me to be a more confident, competent, organised, responsible, and critical researcher. My expectations and plans after my study are: (1) I can implement my knowledge and skill in my workplace, the Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit, Dr Cipto Mangunkusumo Hospital – Faculty of

Medicine, Universitas Indonesia in Jakarta, Indonesia; (2) I will be able to critically identify any health problems and gaps in research and make a systematic and comprehensive strategy to resolve them; (3) I will conduct high-quality research projects in the future and disseminate the results by publications in high-quality peer-reviewed medical journals; and (4) I will initiate more multicentre and international research collaborations.

My journey as a teacher/tutor

I had several opportunities to be involved in teaching or tutoring the medical students at Bond University for EBP and shared decision-making classes. I found these very helpful in improving my skill and confidence in teaching international students since I am also a lecturer for regular and international medical students in my institution, the CEEBM Unit in Jakarta, Indonesia.

I was also involved in several workshops conducted by the IEBH (e.g., EBP, SR) as a co-facilitator. As this is also my regular task in CEEBM, I used this as an opportunity to be involved in international workshops and to be able to teach physicians from different cultural and clinical backgrounds.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AE	Adverse event
AOM	Acute otitis media
AOM-SOS	Acute Otitis Media Severity of Symptom scale
ARI	Acute respiratory infection
BUHREC	Bond University's Human Research Ethics Committee
CEEBM	Clinical Epidemiology and Evidence-Based Medicine
CI	Confidence interval
CMH	Dr Cipto Mangunkusumo Hospital
CREBP	Centre for Evidence-Based Practice
CRF	Case report form
CRM197-PCV7	7-valent Pneumococcal Conjugate Vaccine (PCV) with CRM197
CRSU	Clinical Research Supporting Unit,
EBP	Evidence-Based Practice
e.g.,	'*Exempli gratia'* or 'for example'
ENT	Ear-Nose-Throat
FMUI	Faculty of Medicine Universitas Indonesia
FPS-R	Faces Pain Scale-Revised
GP	General practitioner
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HPA axis	Hypothalamus, pituitary, and adrenal axis
HR	Hazzard ratio
I^2	I² statistic
ICH-GCP	International Conference Harmonization – Good Clinical Practice
i.e.,	'*Id est'* or 'other words'
IEBH	Institute for Evidence-Based Healthcare
ICU	Intensive Care Unit
IL-1ß	Interleukin-1 beta
IL-6	Interleukin-6
ITT	Intention to treat
κ	Kappa statistic

kg	Kilogram
LDXG	Longdan-xiegan
LTB4	Leukotriene B4
M. catarrhalis	*Moraxella catarrhalis*
MD	Mean difference
MEE	Middle ear effusion
mg	Milligram
ml	Millilitre
mm	Millimetre
mmho	Millimho
NNTB	Number needed to treat to benefit
NNTH	Number needed to harm
NSAID	Non-steroidal anti-inflammatory drug
NSI	Nasal saline irrigation
NRS-11	11-point Numeric Rating Scale
OME	Otitis media with effusion
OMPC-PCV7	7-valent PCV with outer membrane protein complex of *Neisseria meningitidi*s serogroup B
OPAL study	Oral Prednisolone for Acute otitis media in chiLdren study
OR	Odds ratio
P	*P* value
PCV	Pneumococcal Conjugate Vaccine
PERHATI-KL	The Indonesian Otorhinolaryngologist and Head-Neck Surgery Society
PHiD-CV11	11-valent PCV conjugated to protein D of *Haemophilus influenzae*
rAOM	Recurrent acute otitis media
RCT	Randomised controlled trial
RR	Relative risk (risk ratio)
RRR	Relative risk reduction
SAA	Static acoustic admittance
SD	Standard deviation
SLBZ	Shenlingbaizhu
SMD	Standardised mean difference
SR	Systematic review

Th1	T helper 1
Th2	T helper 2
TNF-α	Tumor necrosis factor – alpha
VAS	Visual Analogue Scale

CHAPTER 1: GENERAL INTRODUCTION AND THESIS OUTLINE

"There is no one who goes out of his house in order to seek knowledge, but the angels lower their wings in approval of his action."

1.1 INTRODUCTION

1.1.1 ANTIBIOTIC RESISTANCE

Antibiotic resistance is a global public health problem [1]. It is defined as an alteration of the ability of bacteria to survive and grow in the presence of antibiotics aimed at killing or limiting their growth [1-4]. One of the main drivers of antibiotic resistance is antibiotic use [2-5].

Antibiotics are commonly prescribed for infections, such as acute respiratory infection (ARI) [4,6,7]. Acute respiratory infections are frequently found in children, with those under two years of age experiencing up to nine ARI episodes per year [7,8]. Most ARIs are self-limiting and have a low risk of serious complications [8]. Therefore, treatment aims to manage symptoms [8-10]. Antibiotics have consistently been shown to have little or no clinical benefit for ARIs, yet, high rates of antibiotic prescribing continue [9,10]. In Indonesia, a survey study collecting prescriptions of children aged five years and younger with ARIs (2008-2009) demonstrated that 67% of antibiotics were prescribed for these children [11]. In Australian general practice, at least one antibiotic is prescribed for approximately 5.97 million ARI cases annually, which is equivalent to 4.64 out of 8.11 per 100 encounters of new ARI cases [12]. In the United States, the antibiotic prescribing rate for ARIs in primary care (2007-2009) was 62% [13].

1.1.2 ACUTE OTITIS MEDIA

Prevalence, aetiology, and pathogenesis

Acute otitis media (AOM), one type of ARI, is an inflammation of the middle ear with several symptoms such as rapid onset of specific (e.g., ear pain) or non-specific symptoms (e.g., irritability, fevers); and signs such as acute inflammation (e.g., red ear drum) and middle ear effusion (e.g., air fluid level, bulging) [14,15]. It is most common in children younger than two years [16]. Approximately 75% of children in their first five years of life experience an episode of AOM [17]. In East Jakarta (Indonesia), the point prevalence rate of AOM in children aged 2-5 years was 5.4% [18]. In Australia, severe AOM is particularly a problem for indigenous children (7.9%), compared to non-indigenous (1.7%) [19].

Out of all the symptoms of AOM, pain is one of the most distressing for AOM [20]. It is seven times more likely to be found in a child with AOM, compared to a child without.

However, younger children are less likely to complain of ear pain as they are less able to localise the pain [20].

The basic pathogenesis of AOM is an inflammatory mechanism, which can be induced by microbia such as viruses (e.g., respiratory syncytial virus, rhinovirus, influenza virus, adenovirus) and/or bacteria (e.g., *Streptococcus pneumoniae*, *Nontypeable Hemophillus influenzae*, *Moraxella catarrhalis)* [21]. This mechanism is mediated by inflammatory mediators (e.g., cytokines, chemokines, mast cells, prostaglandins, leukotrienes) that are responsible for altering "vascular permeability changes, chemotaxis, stimulation of epithelial secretory activity, enhancement of mucous glycoprotein secretion, and production of other mediators" [22]. Later, inflammation may promote a dysfunction of the eustachian tube resulting in middle ear effusion [23].

Management with antibiotics

Following the introduction of antibiotics for infectious disease, specifically for AOM, rates of complication rapidly declined. Physicians may prescribe antibiotics due to potential complications following AOM, such as spontaneous tympanic membrane perforation, persistent middle ear effusion, and acute mastoiditis [17,24,25]. A Cochrane review demonstrates that antibiotics reduced the number of children who had persistent middle ear effusion at six to eight weeks by 12% (RR 0.88, 95% CI 0.78 to 1.00; NNTB 16) and had tympanic membrane perforations by 63% (RR 0.37, 95% CI 0.18 to 0.76; NNTB 33) [26]. It was originally believed this was due to the routine use of antibiotics and high rates of prescribing antibiotics for AOM have continued [12,27]. Initially, the evidence showed that this antibiotic treatment could be potential as there were 13.7% more children had resolution of AOM symptoms and signs compared to placebo [28]. However, more recent, high quality meta-analyses show that, on average, antibiotics have no effect on pain at Day 1 and minimal at Day 2 [26], although some children are more likely than others to benefit from antibiotics (i.e., children: with severe symptom and signs (e.g., moderate to severe ear pain, fever $\geq 39^{\circ}$ C), aged < two years with bilateral AOM, and/or with tympanic membrane perforation) [14,29].

This introduces a level of uncertainty for clinicians, and guideline developers [30]. In Indonesia, there is inconsistency in treatment guidelines for AOM [31,32]. The Indonesian Otorhinolaryngologist and Head-Neck Surgery Society (PERHATI-KL) guideline

recommends antibiotics only for high risk AOM; however, without clear definitions of "high" and "low risk" AOM [31]. In contrast, the Ministry of Health Republic of Indonesia practice guideline for primary care practitioners recommends antibiotic treatment for all cases of AOM. This is regardless of case severity and dose is differentiated by the severity (lower dose for mild AOM versus higher dose for severe AOM) [32]. This inconsistency potentially leads to differences in antibiotic prescribing for AOM amongst physicians in Indonesia.

Even with the use of antibiotics, 11% to 19% of children with AOM experience persistent symptoms after three to six days [33]. This signifies that we need more effective treatment for AOM.

Alternative treatments for acute otitis media

There is a need for other effective treatments for AOM (e.g., acetaminophen, non-steroidal anti-inflammatory drug [NSAID], decongestants, anaesthetic-analgesic ear drops) [34-36]. Acetaminophen or NSAID, alone or combination, were found to be effective for pain relief in AOM. However, this conclusion was drawn from one study in a Cochrane review of poor-quality evidence [34]. Other common alternative treatments, such as decongestants and/or antihistamines may also be effective in reducing the incidence of persisting AOM. However, they also increase the risk of adverse effects (e.g., diarrhoea, rash, dizziness) up to five to eight times, particularly the decongestant alone [35]. Anaesthetic-analgesic ear drops were found beneficial in reducing pain at Day 2 and antibiotic consumption by Day 8 compared to usual care. However, we are not confident to the result because of a small sample size (did not achieve the sample size target) [36] (see Appendix 1.1 for further details and other potential alternative treatment for AOM).

1.1.3 CORTICOSTEROIDS AS A POTENTIAL ALTERNATIVE TREATMENT FOR ACUTE OTITIS MEDIA

There are theoretical reasons why corticosteroids might be effective. Based on the pathogenesis of AOM, an intervention which suppresses the inflammatory process could have an important role in the resolution of AOM [22]. Corticosteroids play an important role in inhibiting the inflammation process, including the inhibition of the mediators that are involved in inflammatory process in the middle ear [22]. Corticosteroids suppress the immune response to reduce the inflammation by facilitating apoptosis of T lymphocytes and polymorphonuclear leukocytes (i.e., neutrophils, eosinophils, and basophils), suppressing

production of inflammatory cytokines (e.g., IL-1β, TNF-α, IL-6) and cell adhesion molecules, and inhibiting the Th1- and Th2-derived cytokines [37]. Corticosteroids also inhibit inflammatory enzyme activities such as phospholipases, which prevent arachidonic acid from synthesising leukotrienes and prostaglandins, pro-inflammatory mediators [38]. Therefore, corticosteroids are potentially superior as an anti-inflammatory agent compared to NSAIDs. Non-steroidal anti-inflammatory drugs only inhibit cyclooxygenase, an enzyme that mediates arachidonic acid in releasing prostaglandin [38].

Corticosteroids have been widely used in inflammatory and autoimmune diseases in children. However, despite the favourable effect of corticosteroids for inflammation, there are still several potential adverse effects. A systematic review identified several side effects of short-course of corticosteroids (less than two weeks) in children, such as gastrointestinal disturbances (i.e., vomiting, gastritis, nausea), behavioural changes (i.e., mood swings, nervousness), HPA axis suppression, increased blood pressure, hyperglycaemia, weight gain, and decreased bone mineralisation [39]. However, the review included studies that used a range of corticosteroid types and duration. This may have resulted in uncertain results on the important beneficial and harmful effects of corticosteroid [39].

Corticosteroids have also been used for ARIs, such as acute sinusitis, sore throat, acute bacterial meningitis, and chronic otitis media with effusion [33,40-44] (see Table 1).

In acute sinusitis, a Cochrane review of low to moderate quality evidence showed that oral corticosteroids as an addition to antibiotics may improve short-term symptoms (e.g., facial pain) [40] (see Appendix 1.2 for further details).

In acute sore throat, a Cochrane review of moderate to high quality evidence demonstrated that oral corticosteroids (as an addition to antibiotics or monotherapy) may improve pain complete resolution at 24 to 48 hours and reduce the mean time to complete resolution [41]. A recent RCT of adults without initial antibiotic treatment also demonstrated that a single dose oral dexamethasone may be effective in improving the symptom resolution at 48 hours and reduce the initiation of antibiotics [42]. This beneficial effect is also found in a recent systematic review of moderate to high quality evidence [43] (see Appendix 1.2 for further details).

In acute bacterial meningitis, a Cochrane review of high-quality evidence showed that corticosteroids may reduce the incidence of any hearing loss, including severe hearing loss [44].

In addition, one RCT (*n* = 389) testing oral corticosteroids for children aged two to eight years with chronic otitis media with effusion (OME) for minimum three months duration found that oral corticosteroids have no benefit in the resolution of both audiometry and tympanometry findings, as well as the resolution of middle ear effusion at five weeks, six and 12 months [45].

Table 1. Key points of systemic corticosteroids for acute respiratory infections*

Types of ARIs	**Study design**	**Summary**	**Effects**	**Quality of evidence**
Acute sinusitis [40]	SR of RCTs	Adjuvant corticosteroids to antibiotic treatment improved symptoms at 3 to 7 days and 4 to 14 days	Effective	Low to moderate
Sore throat [43]	SR of RCTs	Corticosteroids, as monotherapy or adjuvant to antibiotic treatment, reduced pain to complete resolution at 24 and 48 hours, mean time of pain relief by 4.8 hours, and mean time to complete resolution by 11.1 hours	Effective	Low to high
Croup [46]	SR of RCTs	Parenteral glucocorticoids reduced: (1) croup symptom scores at six, 12, and 24 hours, (2)	Effective	Low to moderate due to substantial heterogeneity

Types of ARIs	Study design	Summary	Effects	Quality of evidence
		length of inpatient stay, and improved symptoms of croup at 12 and 24 hours.		
Bronchiolitis [47]	Overview of SRs	Corticosteroids only slightly improved clinical scores of respiratory distress and did not reduce length of stay for both patients with and without mechanical ventilation, nor mortality	Ineffective	High for clinical score improvement. Low to moderate for other outcomes due to imprecisions and publication bias
Community-acquired pneumonia [48,49]	SR of RCTs	Systemic corticosteroids reduced all-cause mortality, length of stay in ICU, early clinical failure rate, and time to clinical cure.	Effective	Moderate to high
Virus-induced wheezing [50,51]	RCT	Oral prednisolone reduced the duration of respiratory symptoms of cough, noisy breathing, and rhinitis within 2 weeks after discharge, and reduced the length of stay at the emergency department.	Effective	Low risk of bias

Types of ARIs	Study design	Summary	Effects	Quality of evidence
Influenza or influenza-like illness [52]	SR of observational studies	Corticosteroids increased the risk of mortality	Ineffective	Very low due to indication bias and clinical/ statistical heterogeneity
Bacterial meningitis [44]	SR of RCTs	Adjuvant corticosteroids to antibiotic treatment decreased the risks of severe hearing loss, any hearing loss, and short-term neurological sequelae.	Effective	Moderate to high

*For further details see Appendix 1.2. Corticosteroids for acute respiratory infections.
ARIs= acute respiratory infections; ICU= Intensive Care Unit; RCT= randomised controlled trial; SR= Systematic review.

Several studies of corticosteroids for AOM showed inconsistent results regarding the benefits and risks. Given the limitations described above, we still do not know if corticosteroids are effective in improving symptoms, such as ear pain and middle ear effusion, in children with AOM. We also do not know the adverse effects of corticosteroids in this population. Therefore, it is important to identify, assess, and synthesise the quality of existing evidence of corticosteroids for AOM for both the effectiveness and risks, before implementing this treatment in practice.

1.2 RESEARCH AIM

The overall aim is to identify the effectiveness of corticosteroids as a monotherapy for mild AOM and as an addition to antibiotics for severe AOM in children. To address this, we conducted the following four studies:

1.3 RESEARCH QUESTIONS AND OBJECTIVES

1.3.1 RESEARCH QUESTION 1

Are oral corticosteroids effective for children with AOM either as a monotherapy for mild AOM or as an addition to antibiotics for severe AOM?

Objectives: To systematically review the evidence of corticosteroids for AOM in children.

Project or Study 1: Cochrane review of systemic corticosteroids for AOM in children

Publication: Protocol and systematic review were published in *Cochrane Database of Systematic Reviews.*

1.3.2 RESEARCH QUESTION 2

1. How do physicians (i.e., general practitioners, ear-nose-throat specialists, and paediatricians) in DKI Jakarta, Depok, and Bekasi (Indonesia) manage AOM in children?
2. Is it feasible to conduct a clinical trial testing oral corticosteroids for children with AOM in these Indonesian cities?

Objectives:

1. To identify the current management of AOM in children among Indonesian physicians.
2. To assess a feasibility of a large clinical trial of oral corticosteroids for children with AOM in Indonesia.

Project or Study 2: Current management of children with acute otitis media: a feasibility survey for a pragmatic study in Jakarta, Depok, and Bekasi.

Publication: The results paper was published in *Paediatrica Indonesiana*.

1.3.3 RESEARCH QUESTION 3

1. Is it feasible to conduct all pre-specified methods and procedures feasible to be conducted in the main study, which is a large, pragmatic, parallel, randomised, double-blind, placebo-controlled trial of oral prednisolone for children with AOM in Jakarta, Indonesia?
2. Does oral corticosteroid improve middle ear inflammation by reducing MEE in children with AOM, and does the resolution of MEE correlate with pain and other AOM relevant symptoms?

Objectives:

1. To pilot a clinical trial of oral corticosteroids for children with AOM in Indonesia by testing the feasibility of all pre-specified methods and procedures of the main study (e.g., the overall process, resources, management, scientific components) in a smaller study.
2. To assess the efficacy of oral corticosteroids in improving middle ear inflammation by reducing MEE in children with AOM measured using tympanometry.
3. To identify the correlation between the resolution of MEE and pain and other AOM-relevant clinical symptoms.

Project or Study 3: Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, controlled study (OPAL study).

Publication: The protocol paper was published in *Pilot and Feasibility Studies*. The results paper was also submitted to *Pilot and Feasibility Studies* (under review).

1.3.4 RESEARCH QUESTION 4

Are oral corticosteroids effective as a monotherapy for mild AOM and as an addition to antibiotics for severe AOM in improving clinical outcomes and what are common harm related to short-term oral corticosteroids in children?

Objectives: To develop the protocol for a large, pragmatic, parallel, randomised, double-blind, placebo-controlled trial of oral prednisolone for children with AOM in Indonesia, based on the results from conducting a pilot of the OPAL study.

Project or Study 4: Oral prednisolone for acute otitis media in children: a proposed pragmatic, parallel, randomised, double-blind, placebo-controlled study (OPAL study).

Publication: Protocol for a full-scale clinical trial (OPAL study) was submitted for publication as an appendix of the results paper of Study 3 submitted to *Pilot and Feasibility Studies*.

1.4 THESIS OUTLINE

Chapter 1 – General introduction

The first chapter describes a brief background to the research questions which were driven by the need for an effective alternative treatment to antibiotics for children with AOM. We conducted four projects or studies to respond to our research questions. This chapter will help the readers to understand our justification for our research and follow the whole thesis systematically by project.

Chapter 2 – Systemic corticosteroids for acute otitis media in children (Study 1)

This chapter reports on our first study of the thesis, a Cochrane review of systemic corticosteroids for children with AOM (Study 1). This study collected and summarised information from existing RCTs of children who received either systemic corticosteroids or placebo for AOM. We found insufficient evidence to recommend oral corticosteroids for use in clinical practice. This confirmed the requirement for a high-quality clinical trial to assess the effects of oral corticosteroids for children with AOM.

Chapter 3 – Current management of children with acute otitis media: A feasibility survey for a pragmatic study in Jakarta, Depok, and Bekasi (Study 2).

Prior to the implementation of a clinical trial assessing the effects of oral corticosteroids for children with AOM, we conducted two studies to assess the feasibility of our planned clinical trial. This chapter reports on the first of these, a survey of the current management of children with AOM among Indonesian physicians. It also showed that there was a feasible number of physicians who would participate in our planned clinical trial.

Chapter 4 – Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, controlled study / OPAL study (Study 3).

Following our survey, we conducted a pilot study as our third study, which was part two in demonstrating feasibility of the planned RCT. This chapter reports on the feasibility of all study procedures and outcome measures to be conducted successfully in the main study or the full-size RCT. This smaller scale study also identified obstacles during the process by collecting and assessing the feedback from participating healthcare personnel involved in the study, as well as from parents/caregivers of our study participants. We also conducted a mechanistic sub-study as part of this pilot study to identify the efficacy of oral corticosteroids in the resolution of MEE using tympanometry. We also identified whether the resolution of MEE correlates with pain and other AOM-relevant clinical symptoms.

Chapter 5 – Oral prednisolone for acute otitis media in children: a proposed pragmatic, parallel, randomised, double-blind, placebo-controlled study / OPAL study (Study 4).

Our previous studies led us to finalise our protocol for the main study, which is the last study in this thesis (Study 4). Our observations in the pilot study for the implementation of study procedures and outcome measures, as well as all feedback collected in the pilot study assisted us to improve the study design and modify several aspects in the study process to make the main study feasible to be successfully conducted in Jakarta, Indonesia or elsewhere.

Chapter 6 – Conclusions and implications.

This last chapter describes the key results of each study and brings all the studies together to a final conclusion in order to respond to the research questions of the thesis. This chapter also presents the limitations and strengths of the completed studies, which help us to identify the implications for physicians in practice and for future research.

REFERENCES

1. About antimicrobial resistance. In: Antibiotic/antimicrobial resistance (AR/AMR). CDC Centers for Disease Control and Prevention https://www.cdc.gov/drugresistance/about.html. USA updated 10 September 2010.
2. Antibiotic resistance. World Health Organization. http://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance 5 February 2018.
3. Ancillotti M, Eriksson S, Veldwijk J, Fahlquist JN, Andersson DI, Godskesen T. Public awareness and individual responsibility needed for judicious use of antibiotics: a qualitative study of public beliefs and perceptions. BMC Public Health. 2018;18:1153.
4. Tangcharoensathien V, Sommanustweechai A, Chanvatik S, Kosiyaporn H, Tisocki K. Addressing the threat of antibiotic resistance in Thailand: monitoring population knowledge and awareness. WHO South-East Asia Journal of Public Health. September 2018;7(2):73-8.
5. Sarwar MR, Saqib A, Iftikhar S, Sadiq T. Antimicrobial use by WHO methodology at primary health care centers: a cross sectional study in Punjab, Pakistan. BMC Infectious Diseases. 2018;18:492.
6. The Centre for Clinical Practice National Institute for Health and Clinical Excellence (NICE). Respiratory tract infections – antibiotic prescribing: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. National Institute for Health and Clinical Excellence, London; July 2008. NICE Clinical Guideline 69.
7. Linder JA. Antibiotics for treatment of acute respiratory tract infections: decreasing benefit, increasing risk, and the irrelevance of antimicrobial resistance. Clin Infect Dis. 2008;47:744-6.
8. Thompson M, Cohen HD, Vodicka TA, Blair PS, Buckley DI, Heneghan C, et al. Duration of symptoms of respiratory tract infections in children: systematic review. BMJ. 2013:347:f7027 doi: 10.1136/bmj.f7027 (published 11 December 2013).
9. Harris AM, Hicks LA, Qaseem A. Appropriate antibiotic use for acute respiratory tract infection in adults: Advice for high-value care from the American College of Clinicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164:425-34.
10. Oh AL, Hassali MZ, Al-Haddad MS, Sulaiman SAS, Shafie AA, Awaisu A. Public knowledge and attitudes towards antibiotic usage: a cross-sectional study among the general public in the state of Penang, Malaysia. J Infect Dev Ctries. 2011;5(5):338-47.

11. Pudjiarto P, Kurniawan YS, Kresnawati W. (2011). Irrational prescribing pattern for children with upper respiratory tract infection (URTI) in Indonesia. Paper presented at: Third International Conference for Improving Use of Medicines: Informed strategies, effective policies, lasting solutions; November 14-18; Turkey 2011. http://apps.who.int/medicinedocs/documents/s21782en/s21782en.pdf. Accessed June 27, 2016.
12. McCullough AR, Pollack AJ, Hansen MP, Glasziou PP, Looke DFM, Britt HC, et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. The Medical Journal of Australia. 2017;207(2):65-9.
13. Mehrotra A, Gidengil CA, Setodji CM, Burns RM, Linder JA. Antibiotic prescribing for respiratory infections at retail clinics, physician practices, and emergency departments. Am J Manag Care. 2015;21(4):294-302.
14. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. Clinical Practice Guideline: the diagnosis and management of acute otitis media. The American Academy of Pediatrics. Pediatrics. 2013;131:e964-e999.
15. South Australian Child Health Clinical Network. Australian Policy Clinical Guideline South Australian Paediatric Practice Guidelines: Acute Otitis Media in Children. https://www.sahealth.sa.gov.au/wps/wcm/connect/a8910c004329b4dc81b8ed8bf287c74e/Acute+Otitis+Media+in+children_May2014.pdf?MOD=AJPERES&CACHEID=a8910c004329b4dc81b8ed8bf287c74e. Published February 2014. Accessed February 22, 2016.
16. Morris PS, Leach AJ. Managing otitis media: an evidence-based approach. Aust Prescr. 2009;32:155-9.
17. Le Saux N, Robinson JL, Canadian Paediatric Society Infectious Diseases and Immunization Committee. Management of acute otitis media in children six months of age and older. Paediatr Child Health. 2016;21(1):39-44.
18. Umar S, Restuti RD, Suwento R, Priyono H, Mansyur M. The prevalence and risk factors of acute otitis media in children in the municipality of East Jakarta [Prevalensi dan faktor risiko otitis media akut pada anak–anak di kotamadya Jakarta Timur]. http://lib.ui.ac.id/naskahringkas/2015-09/SP-Sakina%20Umar. Published 2013. Accessed February 20, 2016.
19. Gunasekera H, Knox S, Morris P, Britt H, McIntyre P, Craig JC. The spectrum and management of otitis media in Australian Indigenous and non-Indigenous children: a national study. Pediatr Infect Dis J. 2007;26(8):689-92.

20. Pirozzo S, Del Mar C. Chapter 27. Otitis media. In: Moyer VA, eds. Evidence based paediatrics and child health. London: BMJ Books;2000:238-47.
21. Klein JO, Pelton S. Acute otitis media in children: epidemiology, microbiology, clinical manifestations, and complications. Updated 27 June 2018. https://www.uptodate.com/contents/acute-otitis-media-in-children-epidemiology-microbiology-clinical-manifestations-and-complications.
22. Juhn SK, Jung MK, Hoffman MD, Drew BR, Preciado DA, Sausen NJ, et al. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. Clin Exp Otorhinolaryngol. 2008;1(3):117-38.
23. Coticchia JM, Chen M, Sachdeva L, Mutchnick S. New paradigms in the pathogenesis of otitis media in children. Front Pediatr. 2013;1(52):1–7.
24. Neumark T, Ekblom M, Brudin L, Groth A, Eliasson I, Mölstad S, et al. A Spontaneously draining acute otitis media in children: An observational study of clinical findings, microbiology and clinical course. Scand J Infect Dis. 2011 Dec;43(11-12):891-8. doi: 10.3109/00365548.2011.591820.
25. Gribben B, Salkeld LJ, Hoare S, Jones HF. The incidence of acute otitis media in New Zealand children under five years of age in the primary care setting. J Prim Health Care. 2012;4(3):205-12.
26. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database of Syst Rev. 2015;6:CD000219. DOI:10.1002/14651858.CD000219.pub4
27. Henderson J, Valenti L, Miller GC. General practice antibiotic prescribing for management of otitis media in children. Aust Fam Physician. 2016;45(6):363-5.
28. Rosenfeld RM, Vertrees JE, Carr J, Cipolle RJ, Uden DL, Giebink GS, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: metaanalysis of 5400 children from thirty-three randomized trials. J Pediatr. 1994;124:255-67.
29. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368:1429-35.
30. Damoiseaux RAMJ. Antibiotic treatment for acute otitis media: time to think again. CMAJ. 2005;172(5):657-8.
31. Otology Working Group of Indonesian Otorhinolaryngologist Head and Neck Surgeon Society. Guideline of Ear, Nose, and Throat Diseases in Indonesia [Guideline penyakit

THT di Indonesia]. Indonesian Otorhinolaryngologist Head and Neck Surgeon Society, Jakarta; 2007.

32. Ministry of Health Republic of Indonesia. Clinical practice guideline for clinicians in primary healthcare centres. Jakarta: Ministry of Health Republic of Indonesia;2014. Regulatory No. 5 year 2014.
33. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, et al. A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. J Pediatr. 2003;143:377-85.
34. Sjoukes A, Venekamp RP, Van de Pol AC, Hay AD, Little P, Schilder AGM, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD011534. DOI: 10.1002/14651858.CD011534.pub2.
35. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD001727. DOI: 10.1002/14651858.CD001727.pub4.
36. Hay AD, Downing H, Francis NA, Young GJ, Clement C, Harris SD, et al. Anaesthetic-analgesic ear drops to reduce antibiotic consumption in children with acute otitis media: the CEDAR RCT. Health Technol Assess. 2019 Jul;23(34):1-48. doi: 10.3310/hta23340
37. Cruz-Topete D, Cidlowski J. One hormone, two actions: anti- and pro-inflammatory effects of glucocorticoids. Neuroimmunomodulation. 2015;22(1-2):20-32. DOI: 10.1159/000362724. Epub 2014 Sep 12.
38. Section 1 General pathology, Chapter 2 Acute and chronic inflammation. Robbins and Cotran Pathologic basis of Disease. Seventh Edition. Kumar V, Abbas AK, Fausto N. Elsevier Saunders. Philadelphia 2005. ISBN 0-7216-0187-1.
39. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short course oral corticosteroids in children. Arch Dis Child 2016;0:1–6. DOI: https://doi.org/10.1136/archdischild-2015-309522.
40. Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar CB, Perera R, et al. Systemic corticosteroids for acute sinusitis. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD008115. DOI: 10.1002/14651858.CD008115.pub3.
41. Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ. Corticosteroids as standalone or add-on treatment for sore throat. Cochrane Database of

Systematic Reviews 2012, Issue 10. Art. No.: CD008268. DOI: 10.1002/14651858.CD008268.pub2.

42. Hayward GN, Hay AD, Moore MV, Jawad S. Williams N. Effect of oral dexamethasone without immediate antibiotics vs placebo on acute sore throat in adults a randomized clinical trial. JAMA. 2017;317(15):1535-43.
43. Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, Papola D, Lytvyn L, Vandvik PO, et al. Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. BMJ. 2017;358:j3887.
44. Brouwer MC, McIntyre P, Prasad K, Van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD004405. DOI: 10.1002/14651858.CD004405.pub5.
45. Francis NA, Cannings-John R, Waldron CA, Thomas-Jones E, Winfield T, Shepherd V, et al. Oral steroids for resolution of otitis media with effusion in children (OSTRICH): a double-blinded, placebo-controlled randomised trial. Lancet. 2018;392:557-68.
46. Gates A, Gates M, Vandermeer B, Johnson C, Hartling L, Johnson DW, et al. Glucocorticoids for croup in children. Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD001955. DOI: 10.1002/14651858.CD001955.pub4.
47. Alarcón-Andrade G, Cifuentes L. Should systemic corticosteroids be used for bronchiolitis? Medwave 2018 May-Jun;18(3):e7206 doi: 10.5867/medwave.2018.03.7206.
48. Huang J, Guo J, Li H, Huang W, Zhang T. Efficacy and safety of adjunctive corticosteroids therapy for patients with severe community-acquired pneumonia: a systematic review and meta-analysis. Medicine (Baltimore). 2019;98(13):e14636. DOI: 10.1097/MD.0000000000014636.
49. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD007720. DOI: 10.1002/14651858.CD007720.pub3.
50. Jartti T, Nieminen R, Vuorinen T, Lehtinen P, Vahlberg T, Gern J, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. J Allergy Clin Immunol. 2015;135:691-8.
51. Foster SJ, Cooper MN, Oosterhof S, Borland ML. Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomised, double-blind, placebo-controlled trial. Lancet. 2018;6:97-106.

52. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD010406. DOI: 10.1002/14651858.CD010406.pub2.

CHAPTER 2: SYSTEMIC CORTICOSTEROIDS FOR ACUTE OTITIS MEDIA IN CHILDREN (STUDY 1)

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD012289. DOI: 10.1002/14651858.CD012289.
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012289/full

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD012289. DOI: 10.1002/14651858.CD012289.pub2.

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012289.pub2/full

2.1 Summary

As mentioned in Chapter 1, existing studies have shown inconsistent evidence regarding the effects of corticosteroids in improving clinical symptoms of acute otitis media (AOM) in children, particularly for reducing pain. To address this, we systematically compiled and assessed all available randomised clinical trials (RCTs) which tested systemic corticosteroids for AOM in children. Systematic reviews of RCTs are the highest-level of evidence for interventions. Therefore, we conducted a Cochrane review of RCTs of children aged six months to 12 years with AOM who received either systemic corticosteroids or placebo. We assessed the effects of corticosteroids in: (1) improving pain severity, (2) reducing the duration of pain and other AOM symptoms, (3) improving middle ear effusion, (4) reducing the complications of AOM (e.g., tympanic membrane perforation, mastoiditis), (5) AOM recurrence, and (6) adverse effects of corticosteroids.

This Cochrane review identified two studies of low to very low-quality, meaning the effects of systematic corticosteroids on important clinical outcomes in AOM, such as in the resolution of ear pain and other AOM symptoms, middle ear effusion, as well as AOM recurrence and complications, are uncertain. This review was also not able to provide sufficient information on adverse effects of corticosteroids. A large, high-quality clinical trial is therefore required to resolve the question.

However, since the studies in our Cochrane review only included children with severe AOM who received antibiotic treatment, the results of the review should be translated to the population with severe AOM. Since most AOM cases are mild, it is crucial to identify the effectiveness of systemic corticosteroids for children with mild or uncomplicated AOM who do not require initial antibiotic treatment. To support this, a clear guideline in diagnosing AOM (mild and severe) including evidence-based treatment is required, particularly in the primary care setting.

Cochrane Library

Cochrane Database of Systematic Reviews

Systemic corticosteroids for acute otitis media in children (Protocol)

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB.
Systemic corticosteroids for acute otitis media in children.
Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD012289.
DOI: 10.1002/14651858.CD012289.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Systemic corticosteroids for acute otitis media in children

Respati W Ranakusuma[1], Yupitri Pitoyo[1], Eka D Safitri[1], Sarah Thorning[2], Elaine M Beller[3], Sudigdo Sastroasmoro[4], Chris B Del Mar[3]

[1]Clinical Epidemiology & Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital - Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia. [2]GCUH Library, Gold Coast University Hospital, Southport, Australia. [3]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Gold Coast, Australia. [4]Department of Pediatrics, Dr. Cipto Mangunkusumo Hospital - Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

Contact address: Respati W Ranakusuma, Clinical Epidemiology & Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital - Faculty of Medicine Universitas Indonesia, 2nd Floor Building H, Jl. Diponegoro 71, Jakarta, 10430, Indonesia. anggiranakusuma@yahoo.com.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 7, 2016.

Citation: Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD012289. DOI: 10.1002/14651858.CD012289.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of corticosteroids, with and without antibiotics, for AOM in children.

BACKGROUND

Description of the condition

Acute otitis media (AOM) is a common complication of an acute respiratory infection (ARI); it mostly affects children aged six to 12 months (Lieberthal 2013; SACHCN 2014).

A 2015 update of a clinical practice guideline on the diagnosis and management of AOM states that "Clinicians should diagnose AOM in children who present with moderate-to-severe bulging of the tympanic membrane or new onset of otorrhoea not due to acute otitis externa; and may diagnose AOM in children who present with mild bulging of the tympanic membrane and recent (< 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the tympanic membrane" (Pichichero 2015). The 2014 New South Wales Health (Australia) clinical practice guideline defines AOM as an "acute onset of middle ear inflammation characterised by 1) distinct otalgia (ear pain) that interferes with normal activity or sleep; 2) bulging tympanic membrane and erythema; and 3) possible perforation and otorrhoea (ear discharge)" (NSW Health 2014).

In young children aged from six months to three years the overall incidence of AOM as a complication of ARIs (mostly caused by rhinovirus and adenovirus) was shown to be 37% in a prospective, longitudinal cohort study (Chonmaitree 2008). Fifty per cent of acute symptoms (pain and systemic symptoms) resolve within 24 hours and 80% within 72 hours. Children aged up to two years often experience more severe and protracted illness (Chonmaitree 2008). Studies from Europe and the US have reported that 62% of children aged up to 12 months, and 83% of children aged between one and three years, experience at least one episode of AOM. Among these children, between 10% and 30% experience

recurrent AOM, and 2% to 25% experience persistent middle ear effusion for three months, many requiring ventilation tube (grommet) insertion (Gribben 2012; Kitamura 2015).

The prevalences of AOM are slightly varied across Asian countries. In Korea, a 1991 national survey reported a point prevalence of 0.08% for AOM in children aged up to 15 years (Lee 2012); in Malaysia, 9% of children aged from three months to 12 years experienced AOM over the previous three years (Tikaram 2012). A 2005 study in Taiwan found that 13.2% of children aged up to seven years had experienced AOM (Ting 2012). In East Jakarta, Indonesia, the point prevalence of AOM in children aged from two to five years was 5.4% (Umar 2013).

As the risk of AOM increases in the indigenous population, a cluster survey in Indigenous versus non-Indigenous children in Australia found that severe otitis media was more prevalent in Indigenous children (7.9%) compared to non-Indigenous children (1.7%) (Gunasekera 2007).

Pain is one of the most common and distressing symptoms of AOM. Many clinical practice guidelines have recommended analgesic (e.g. paracetamol, ibuprofen) as an initial treatment option for pain management in AOM (Lieberthal 2013; NSW Health 2014; SACHCN 2014). A study on the use of ibuprofen versus acetaminophen and placebo for the symptoms of AOM in children showed no significant differences between treatment groups in the improvement of tympanic membrane inflammation, rectal temperature, appetite, sleep and playing activity 48 hours after treatment (Bertin 1996). However, there was a modest benefit of ibuprofen over placebo in reducing pain. There was no significant difference between acetaminophen and placebo. Topical analgesics have limited evidence of efficacy in reducing ear pain (Foxlee 2011).

Antibiotics are also commonly prescribed in the treatment for AOM. Antibiotics have a modest effect in reducing pain at two to three days, with a number needed to treat to benefit (NNTB) of 20 children (Venekamp 2015). Despite using antibiotics, 11% to 19% of children with AOM experience persistent symptoms for more than six days (Lieberthal 2013). Ear effusions may persist in 30% to 60% of children for up to one month, and in 15% to 25% of children for up to three months (Chonmaitree 2003). Almost one-third of these children do not have bacterial growth from their MEE. One-third of affected children experience recurrence within a month (Chonmaitree 2003). Nevertheless, the clinical practice guideline of the American Academy of Pediatrics strongly recommends antibiotics for children aged six months and older with bilateral or unilateral AOM and severe signs or symptoms. Antibiotics are also recommended for children younger than two years with bilateral AOM without severe signs or symptoms (Lieberthal 2013).

An alternative strategy for the management of AOM in children is close observation through follow-up, based on joint decision-making with the parent or caregiver. However, close observation requires accessible follow-up and continuity of care (Lieberthal 2013; Pichichero 2015). Observation alone may not be suitable for high-risk or vulnerable populations such as Indigenous children in remote settings or those with complications such as cleft palate, Down syndrome or immunodeficiency syndromes (Morris 2009; NSW Health 2014).

Other treatments, such as decongestants or antihistamines, are not recommended for children due to the risk of adverse events and the lack of benefit. There is limited evidence on the use of decongestant/antihistamine combinations for AOM in children: a Cochrane review found a small statistical benefit from the combination medication, but the clinical significance was minimal and the contributing studies may have been biased (Coleman 2008). However, the 2015 Japanese clinical practice guideline on the diagnosis and management of AOM in children recommended use of complementary nasal treatment for children with AOM associated with nasal disease (Kitamura 2015). A study on the use of intranasal steroid spray (triamcinolone acetonide) for otitis media with effusion and negative middle ear pressure showed there was no statistically significant difference in the normalization of the tympanometric findings between intranasal steroid group and placebo in six weeks (Gluth 2011). A Cochrane review on the use of topical intranasal steroids for otitis media effusion in children also found no evidence of benefit in terms of symptoms (including ear symptoms that are crucial in the management of AOM) either at short- or longer-term follow-up (Simpson 2011).

Description of the intervention

Corticosteroids are natural steroid hormones produced by the adrenal cortex, which can be synthetically manufactured. They have an important anti-inflammatory role (Gupta 2008), and they have been used for a wide range of both acute and chronic inflammatory illnesses in adults and children (Coutinho 2011).

There are concerns about the possible risks associated with corticosteroid use, such as increased appetite, weight gain, fluid retention, gastritis, headache, mood swings, increased blood glucose and Addisonian crisis from abrupt stopping of the corticosteroid, all of which can occur with protracted use. However, in general, short-term use (one week or less) does not cause these harms or require dose-tapering (Deshmukh 2007). A randomised controlled trial (RCT) of corticosteroids for AOM found no correlation between the emergence of viral infection and corticosteroid use (Chonmaitree 2003). A Cochrane review on the use of systematic corticosteroids for acute sinusitis found no serious side effects (Venekamp 2014).

How the intervention might work

Persistent middle ear effusion (MEE) after resolution of AOM is a concern. MEE has been found in 60% to 70% of children two weeks after successful antibiotic treatment of AOM. Presentation

decreases to 10% to 25% at three months, but in 5% to 10% of cases MEE is present one year later (Lee 2012; Lieberthal 2013; Lighthall 2015; Mahadevan 2012; Rosenfeld 2001). One cause of MEE is dysfunction of the Eustachian tube due to the inflammation process. The Eustachian tube has an important role in maintaining ventilation and protecting the middle ear cavity, and in the drainage of middle ear fluid (Coticchia 2013). MEE is also caused by dysfunction of the epithelial sodium channel (ENaC) in controlling the periciliary fluid that is essential for maintaining a fluid-free middle ear cavity. An in vitro study showed that interleukin-1β (IL-1β), an important inflammatory cytokine mostly found in the MEE, inhibits fluid absorption by suppressing ENaC in various epithelia including airway epithelial cells (Choi 2006; Choi 2007).

Despite the benefits of using antibiotics for some ear infections, they have several consequences due to bacterial death and the release of inflammatory bacterial products. This may induce and prolong inflammation in the middle ear and lead to otitis media with effusion (OME) and further episodes of AOM (Principi 2013). This suggests that the inflammatory mechanism may be involved in the basic pathogenesis of AOM. This mechanism is induced by both cellular and chemical mediators in the middle ear. These mediators (i.e. cytokines, chemokines, mast cells, prostaglandins, leukotrienes) contribute by altering vascular permeability, increasing mucous glycoprotein secretion and stimulating the chemotaxis process, epithelial secretion activity and other mediators (Juhn 2008).

Based on this pathogenesis, an intervention that suppresses the inflammatory process could have an important role in the resolution of AOM, including inhibition of the interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α) early-response cytokines that are commonly found in children. Corticosteroids play an important role in inhibiting the inflammation process through genomic and non-genomic mechanisms, including inhibition of mediators that are involved in middle ear inflammatory processes (Juhn 2008). An animal study showed that AOM inflammatory disease generally peaks between three and five days and resolves by 10 to 14 days (MacArthur 2006). However, a randomised controlled trial (RCT) has shown no significant clinical benefits of the use of corticosteroids for AOM (Chonmaitree 2003). A temporary improvement in tympanometry in patients who received corticosteroids suggested the possibility that discontinuation after a five-day course of corticosteroid induced a rebound effect due to ongoing middle ear inflammation, which indicated the need for a longer duration of treatment (Chonmaitree 2003).

Corticosteroids have been found to be effective in some ARIs, for example when combined with antibiotics for patients with sore throat (Hayward 2012). A recent study has shown that the use of oral corticosteroids as an additional treatment to antibiotics for AOM with discharge through tympanostomy tubes shortened the duration of otorrhoea (McCormick 2003). However, a few small trials on the use of corticosteroids as an additional treatment to antibiotics for AOM in children have reported varied results (Wang 2007).

As a monotherapy, oral corticosteroids are not effective for adults with clinically diagnosed acute sinusitis (Venekamp 2014). Nevertheless, when combined with antibiotics, oral corticosteroids may have a modest beneficial effect (Venekamp 2014). An RCT also reported no significant difference between oral prednisolone as a standalone therapy and placebo in hospitalised patients with acute viral mild-to-moderate wheezing (Panickar 2009). However, as close observation (without antibiotic administration) is a treatment option for AOM, there is a risk of persistent and recurrent AOM in some cases, and there is involvement of an inflammatory mechanism in the middle ear, it is worthwhile identifying the effects of corticosteroids as a monotherapy for AOM in children.

Why it is important to do this review

The therapeutic options for the management of AOM in children are currently unsatisfactory. An effective treatment modality is needed and systemic corticosteroids may fill that role, either as a monotherapy or in addition to antibiotics. A recent literature review concluded that there was insufficient evidence to recommend corticosteroids for AOM (Principi 2013). However, potentially relevant studies were not included in that review and therefore there is need for a further systematic assessment (McCormick 2003; Ruohola 1999; Wang 2007). An up to date Cochrane review is warranted to assess the effects of corticosteroids, as another treatment option, for the treatment of AOM in children.

OBJECTIVES

To assess the effects of corticosteroids, with and without antibiotics, for AOM in children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs).

Types of participants

We will include children aged up to 15 years with AOM. AOM often correlates with immaturity of the immune system, therefore we will set the age limit at 15 years because maturation of the B-

cells involved in the immune system commences at that point and beyond (McKenna 2001).

AOM is defined as "the rapid onset of ear pain accompanied with bulging and/or hyperaemic tympanic membrane and the presentation of middle ear effusion" (Lieberthal 2013; Pichichero 2015).

We will include both unilateral and bilateral AOM. Participants will be included irrespective of the setting from which they were recruited.

We will exclude children with contraindications to corticosteroid therapy (e.g. immunodeficient or immunocompromised, or both), children with anatomic or physiological disorders of the ear or nasopharynx and those with chronic MEE. We will also exclude children with ventilation tubes because this procedure is principally used for non-acute (chronic) otitis media with effusion.

Types of interventions

We will include studies that compare any type of systemic corticosteroids (e.g. oral, parenteral) with placebo, either without antibiotics (i.e. corticosteroid versus placebo) or with antibiotics (i.e. antibiotics plus corticosteroid versus antibiotics plus placebo).

We will exclude studies using any type of topical corticosteroids (e.g. intranasal).

For symptomatic treatment, patients may have received acetaminophen as an antipyretic and analgesic treatment (Bertin 1996).

Types of outcome measures

Primary outcomes

1. Proportion of children with pain at various time points (24 hours; two to three days; and four to seven days - time points taken from Venekamp 2015).
2. Reduction of overall or specific symptoms (e.g. ear discomfort, hearing loss, irritability, sleep disturbance, diminished appetite). Reduction of overall or specific symptoms may be measured using visual analogue scales or validated symptom scales specific to otitis media such as the Acute Otitis Media Severity of Symptoms Scale (AOM-SOS), Otitis Media Outcome-22 questionnaire (OMO-22), Otitis Media-6 quality of life survey (OM-6), or others (Timmerman 2007).
3. Reduction in overall or specific symptom duration.
4. Adverse effects.

Secondary outcomes

1. Changes in tympanometry measurements at various time points as an objective assessment of the resolution of AOM (e.g. middle ear pressure, tympanogram curve types).
2. Tympanic membrane perforation.
3. Contralateral otitis (in children with unilateral infection).
4. AOM recurrence, which is defined as the occurrence of AOM episodes within one month after completion of antibiotic therapy (Pichichero 2000).
5. Serious complications related to AOM such as mastoiditis and meningitis.

Search methods for identification of studies

Electronic searches

We will search the following databases from inception to the present:

1. Cochrane Central Register of Controlled Trials (CENTRAL);
2. MEDLINE (Ovid);
3. Embase (Elsevier);
4. CINAHL (EBSCO);
5. Web of Science (Thomson Reuters); and
6. LILACS (BIREME).

We will combine the search terms set out in Appendix 1 with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011). We will assess whether we need to apply a filter for retrieving studies in children (Boluyt 2008). This will depend on the number of search results retrieved. We will not impose language or publication restrictions.

Searching other resources

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will check the reference lists of all primary studies and review articles for additional references. We will contact experts in the field to identify additional unpublished materials.

Data collection and analysis

Selection of studies

Three review authors (RR, YP, EDS) will independently screen the titles and abstracts of all potential studies identified as a result of the searches. We will retrieve full-text study reports of potentially relevant studies. Three review authors (RR, YP, EDS) will independently screen the retrieved reports to identify studies for inclusion and they will record the reasons for exclusion of ineligible studies. We will resolve disagreements through discussion or, if required, consult with a third review author (EMB or CDM). We

will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is assessed in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2010).

Data extraction and management

We will use a data collection form, which has been piloted on at least one study in the review, to collate study characteristics and outcome data. Three review authors (RR, YP, EDS) will independently extract study characteristics from included studies. We will extract the following study characteristics:

1. methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study;
2. participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria;
3. interventions: intervention, comparison, concomitant medications and excluded medications;
4. outcomes: primary and secondary outcomes specified and collected, and time points reported; and
5. notes: funding for trial and notable conflicts of interest of trial authors.

Three review authors (RR, YP, EDS) will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus. A review author (RR) will input data into the Review Manager software (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. Two review authors (YP, EDS) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Three review authors (RR, YP, EDS) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion with another review author (EMB or CDM). We will assess the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

We will grade each potential source of bias as high, low or unclear and we will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes, where necessary. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

We will take into account the risk of bias for the studies that contribute to that outcome when considering treatment effects.

Measures of treatment effect

We will enter the outcome data for each study into the data tables in RevMan 2014 to calculate the treatment effects. We will use the risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and the mean difference (MD) or standardised mean difference (SMD) for continuous outcomes.

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

Unit of analysis issues

We do not expect any trials in this area to have applied cross-over or cluster-randomised designs.

For studies with more than two intervention groups, where more than two of the groups are eligible for this review, we will follow the methods in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). That is, in studies with more than one control group or more than one intervention group, we will combine the results of the control or intervention groups, respectively.

Dealing with missing data

We will contact trial authors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results using the 'Risk of bias' assessment.

If numerical outcome data are missing, such as standard deviations (SDs) or correlation coefficients, and they cannot be obtained from the trial authors, we will calculate the missing parameters from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If values are imputed (e.g. correlation coefficients), rather than calculated, we will perform sensitivity analyses to assess how sensitive the results are to reasonable changes in the assumptions that are made in the imputation.

Assessment of heterogeneity

We will use the Chi² test and the I² statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity (over 50% as explained in the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011), we will report this and explore the possible causes by conducting prespecified subgroup analysis. Nonetheless, we are aware that there is uncertainty in the I² statistic measurement when there are few studies in a meta-analysis. In that case, we will use a P value of 0.10 rather than 0.05 in the Chi² test to determine statistical heterogeneity (Higgins 2011).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will pool data from studies that we judge to be clinically homogeneous using RevMan 2014, with a fixed-effect model. If a single true effect is not plausible, due to variation in populations and interventions or substantial heterogeneity, we will use a random-effects model instead (DerSimonian and Laird method) (Higgins 2011). If more than one study provides usable data in any single comparison, we will perform a meta-analysis. We will analyse primary outcomes at three time points, namely 24 hours; two to three days; and four to seven days.

GRADE and 'Summary of findings' table

We will create a 'Summary of findings' table using the following primary outcomes: proportion of children with pain at various time points (24 hours; two to three days; and four to seven days); reduction of overall or specific symptoms; reduction in overall or specific symptom duration; and adverse effects of corticosteroids. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004; GRADE 2004). We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEproGDT software (GRADEproGDT 2015). We will justify all decisions to downgrade or upgrade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses if there are sufficient studies:

1. short- versus long-term use of corticosteroids ($\leq$ one week versus > one week);
2. type of corticosteroids (i.e. prednisolone, dexamethasone, etc.); and
3. corticosteroids as monotherapy versus adjuvant to antibiotics.

We will use the Chi² test to test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to carry out sensitivity analyses by identifying and excluding studies with high risk of bias or low methodological quality based on the Cochrane 'Risk of bias' assessment, if there are sufficient included studies to make this feasible.

ACKNOWLEDGEMENTS

This review is an unfunded project and part of a Master of Science by Research Program Project at the Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia. It is supported by the Centre for Research in Evidence-Based Practice, Bond University.

We would especially like to thank Clare Dooley and Liz Dooley for their assistance in the preparation of the protocol. We would also like to thank the review panel of the Cochrane Acute Respiratory Infections Group for their support and constructive feedback.

The methods section of this protocol is based on a standard template developed by Cochrane Airways and adapted by Cochrane Acute Respiratory Infections.

We wish to thank the following people for commenting on the draft protocol: Jean Symes, Zaina AlBalawi, Brian Westerberg, Simona Nistor-Grahl, Ravi Shankar and Michelle Guppy.

Additional references

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**(7454):1490.

Bertin 1996

Bertin L, Pons G, d'Athis P, Duhamel JF, Maudelonde C, Lasfargues G, et al. A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media. *Fundamental & Clinical Pharmacology* 1996;**10**(4): 387–92.

Boluyt 2008

Boluyt N, Tjosvold L, Lefebvre C, Klassen TP, Offringa M. Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. *Archives of Pediatrics and Adolescent Medicine* 2008;**162**(2):111–6. [DOI: 10.1001/archpediatrics.2007.40]

Choi 2006

Choi JY, Son EJ, Kim JL, Lee JH, Park HY, Kim SH, et al. ENaC- and CFTR-dependent ion and fluid transport in human middle ear epithelial cells. *Hearing Research* 2006; **211**(1-2):26–32.

Choi 2007

Choi JY, Choi YS, Kim SJ, Son EJ, Choi H, Yoon JH. Interleukin-1β suppresses epithelial sodium channel β-subunit expression and ENaC-dependent fluid absorption in human middle ear epithelial cells. *European Journal of Pharmacology* 2007;**567**(1-2):19–25.

Chonmaitree 2003

Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH. A randomized, placebo-controlled trial of the effect of antihistamine of corticosteroid treatment in acute otitis media. *Journal of Pediatrics* 2003;**143**(3): 377–85.

Chonmaitree 2008

Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, et al. Viral upper respiratory tract infection and otitis media complication in young children. *Clinical Infectious Diseases* 2008;**46**(6):815–23. [DOI: 10.1086/528685.]

Coleman 2008

Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD001727.pub4]

Coticchia 2013

Coticchia JM, Chen M, Sachdeva L, Mutchnick S. New paradigms in the pathogenesis of otitis media in children. *Frontiers in Pediatrics* 2013;**1**(52):1–7.

Coutinho 2011

Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Molecular and Cellular Endocrinology* 2011;**335**(1):2–13.

Deshmukh 2007

Deshmukh CT. Minimizing side effects of systemic corticosteroids in children. *Indian Journal Dermatology, Venereology and Leprology* 2007;**73**(4):218–21.

Foxlee 2011

Foxlee R, Johansson AC, Wejfalk J, Dooley L, Del Mar CB. Topical analgesia for acute otitis media. *Cochrane Database of Systematic Reviews* 2011, Issue 8. [DOI: 10.1002/14651858.CD005657.pub2]

Gluth 2011

Gluth MB, McDonald DR, Weaver AL, Bauch CD, Beatty CW, Orvidas LJ. management of Eustachian tube dysfunction with nasal steroid spray. *Archives Otolaryngology - Head Neck Surgery* 2011;**137**(5):449–55.

GRADE 2004

GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

GRADEproGDT 2015 [Computer program]

McMaster University (developed by Evidence Prime, Inc.). GRADEproGDT: GRADEpro Guideline Development Tool [www.guidelinedevelopment.org]. Hamilton: McMaster University (developed by Evidence Prime, Inc.), 2015.

Gribben 2012

Gribben B, Salkeld LJ, Hoare S, Jones HF. The incidence of acute otitis media in New Zealand children under five years of age in the primary care setting. *Journal of Primary Health Care* 2012;**4**(3):205–12.

Gunasekera 2007

Gunasekera H, Knox S, Morris P, Britt H, McIntyre P, Craig JC. The spectrum and management of otitis media in Australian Indigenous and non-Indigenous children: a national study. *Pediatric Infectious Disease Journal* 2007;**26** (8):689–92.

Gupta 2008

Gupta P, Bhatia V. Corticosteroid physiology and principles of therapy. *Indian Journal of Pediatrics* 2008;**75**(10): 1039–44.

Hayward 2012

Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ. Corticosteroids as standalone or add-on treatment for sore throat. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: 10.1002/14651858.CD008268.pub2]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Juhn 2008
Juhn SK, Jung MK, Hoffman MD, Drew BR, Preciado DA, Sausen NJ, et al. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. *Clinical and Experimental Otorhinolaryngology* 2008;**1**(3):117–38.

Kitamura 2015
Kitamura K, Iino Y, Kamide Y, Kudo F, Nakayama T, Suzuki K, et al. Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan - 2013 update. *Auris Nasus Larynx* 2015;**42**(2): 99–106.

Lee 2012
Lee HJ, Park SK, Choi KY, Park SE, Chun YM, Kim KS, et al. Korean clinical practice guidelines: otitis media in children. *Journal of Korean Medical Science* 2012;**27**(8): 835–48.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lieberthal 2013
Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. *Pediatrics* 2013;**131**(3): e964–e99.

Lighthall 2015
Lighthall JG, Kempton JB, Hausman F, MacArthur CJ, Trune DR. Control of middle ear inflammatory and ion homeostasis genes by transtympanic glucocorticoid and mineralocorticoid treatments. *PloS One* 2015;**10**(3):1–15. [DOI: 10.1371/journal.pone.0119228]

MacArthur 2006
MacArthur CJ, Hefeneider SH, Kempton JB, Parrish SK, McCoy SL, Trune DR. Evaluation of the mouse model for acute otitis media. *Hearing Research* 2006;**219**(1-2):12–23.

Mahadevan 2012
Mahadevan M, Navarro-Locsin G, Tan HKK, Yamanaka N, Sonsuwan N, Wang PC, et al. A review of the burden of disease due to otitis media in the Asia-Pacific. *International Journal of Pediatric Otorhinolaryngology* 2012;**76**(5):623–35.

McCormick 2003
McCormick DP, Saeed K, Uchida T, Baldwin CD, Deskin R, Lett-Brown MA, et al. Middle ear fluid histamine and leukotriene B4 in acute otitis media: effect of antihistamine or corticosteroid treatment. *International Journal of Pediatric Otorhinolaryngology* 2003;**67**(3):221–30.

McKenna 2001
McKenna RW, Washington LT, Aquino DB, Picker LJ, Kroft SH. Immunophenotypic analysis of hematogones (B-lymphocyte precursors) in 662 consecutive bone marrow specimens by 4-color flow cytometry. *Blood* 2001;**98**(8): 2498–507.

Moher 2010
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International Journal of Surgery* 2010;**8**(5):336–41.

Morris 2009
Morris PS, Leach AM. Managing otitis media: an evidence-based approach. *Australian Prescriber* 2009;**32**(6):155–9.

NSW Health 2014
NSW Health. Otitis media: acute management of sore ear (clinical practice guideline). Infants and children: Otitis media, acute management of sore ear (second edition) 2014; Vol. Available from: http://www0.health.nsw.gov.au/policies/gl/2014/pdf/GL2014_023.pdf.

Panickar 2009
Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *New England Journal of Medicine* 2009;**360**(4):329–38.

Pichichero 2000
Pichichero ME. Recurrent and persistent otitis media. *Pediatric Infectious Diseases Journal* 2000;**19**(9):911–6.

Pichichero 2015
Pichichero ME, Casey JR. Acute otitis media: Update 2015. http://contemporarypediatrics.modernmedicine.com/contemporary-pediatrics/news/acute-otitis-media-update-2015 2015.

Principi 2013
Principi N, Bianchini S, Baggi E, Esposito S. No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media. *European Journal of Clinical Microbiology and Infectious Diseases* 2012;**32**(2):151–60.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rosenfeld 2001
Rosenfeld RM. Observation option toolkit for acute otitis media. *International Journal of Pediatric Otorhinolaryngology* 2001;**58**(1):1–8.

Ruohola 1999
Ruohola A, Heikkinen T, Jero J, Puhakka T, Juven T, Närkiö-Mäkelä M, et al. Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tymapnostomy tubes. *The Journal of Pediatrics* April 1999;**134**:459–63.

SACHCN 2014
South Australian Child Health Clinical Network. Acute otitis media in children. South Australian Paediatric Practice Guidelines (available from http://www.sahealth.sa.gov.au/) 2014:1–10.

Simpson 2011
Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with

otitis media with effusion in children. *Cochrane Database of Systematic Reviews* 2011, Issue 5. [DOI: 10.1002/14651858.CD001935.pub3]

Tikaram 2012
Tikaram A, Chew YK, Zulkiflee AB, Chong AW, Prepageran N. Prevalence and risk factors associated with otitis media with effusion in children visiting tertiary care centre in Malaysia. *International Medical Journal Malaysia* 2012;**11**(1):37–40.

Timmerman 2007
Timmerman AA, Meesters CMG, Speyer R, Anteunis LJC. Psychometric qualities of questionnaires for the assessment of otitis media impact. *Clinical Otolaryngology* 2007;**32**(6):429–39.

Ting 2012
Ting PJ, Lin CH, Huang FL, Lin MC, Hwang KP, Huang YC, et al. Epidemiology of acute otitis media among young children: a multiple database study in Taiwan. *Journal of Microbiology, Immunology and Infection* 2012;**45**(6):453–8.

Umar 2013
Umar S, Restuti RD, Suwento R, Priyono H, Mansyur M. The prevalence and risk factors of acute otitis media in children in the municipality of East Jakarta [Prevalensi dan faktor risiko otitis media akut pada anak–anak di kotamadya Jakarta Timur]. http://lib.ui.ac.id/naskahringkas/2015-09/SP-Sakina%20Umar 2013.

Venekamp 2014
Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar CB, Perera R, et al. Systemic corticosteroids for acute sinusitis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD008115.pub3]

Venekamp 2015
Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD000219.pub4]

Wang 2007
Wang C, Liu Z, Huang X, Xu K. The curative effect of corticosteroid on acute otitis media with middle ear effusion [Chinese]. *Journal of Clinical Otorhinolaryngology, Head and Neck Surgery [Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi]* 2007;**21**(4):167–8.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

MEDLINE (Ovid)
1 exp Otitis Media/ (22799)
2 otitis media.tw. (17913)
3 (middle ear adj5 (infect* or inflam*)).tw. (1878)
4 (ome or aom).tw. (7702)
5 or/1-4 (33474)
6 exp Adrenal Cortex Hormones/ (355953)
7 adrenal cortex hormone*.tw,nm. (56917)
8 corticosteroid*.tw,nm. (83470)
9 corticoid*.tw,nm. (5657)
10 steroid*.tw,nm. (284604)
11 glucocorticoid*.tw,nm. (92417)
12 exp Pregnenediones/ (173193)
13 pregnenedione*.tw,nm. (2108)
14 pregnenolone*.tw,nm. (6726)
15 hydrocortisone.tw,nm. (70460)
16 hydroxypregnenolone.tw,nm. (928)
17 tetrahydrocortisol.tw,nm. (471)
18 cortodoxone.tw,nm. (779)
19 cortisone.tw,nm. (22609)
20 corticosterone.tw,nm. (30378)
21 triamcinolone.tw,nm. (10351)

22 prednisone.tw,nm. (47956)
23 prednisolone.tw,nm. (41014)
24 paramethasone.tw,nm. (246)
25 methylprednisolone.tw,nm. (22772)
26 dexamethasone.tw,nm. (62108)
27 clobetasol.tw,nm. (1395)
28 beclomethasone.tw,nm. (3662)
29 betamethasone.tw,nm. (6960)
30 budesonide.tw,nm. (5108)
31 (efcortesol or hydrocortone or solu-cortef).tw,nm. (35)
32 (betnelan or betnesol).tw,nm. (25)
33 (deflazacort or calcort).tw,nm. (486)
34 (medrone or solu-medrone or depo-medrone).tw,nm. (17)
35 kenalog.tw,nm. (185)
36 (novolizer or pulmicort or symbicort).tw,nm. (328)
37 (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm. (287)
38 cortisol.tw,nm. (51031)
39 or/6-38 (712225)
40 5 and 39 (1017)

CONTRIBUTIONS OF AUTHORS

Respati W Ranakusuma (RR) drafted the protocol and will contribute as a primary review author, select studies for inclusion, extract data, enter data into RevMan, and carry out and interpret the analysis.

Eka Dian Safitri (EDS) will select studies for inclusion and extract data.

Yupitri Pitoyo (YP) will select studies for inclusion and extract data.

Sarah Thorning (ST) will develop and run the search strategy, and obtain copies of studies.

Elaine M Beller (EMB) will carry out and interpret the analysis, contribute as the third review author for disagreements on methodological/statistical issues and check the correct use of grammar.

Sudigdo Sastroasmoro (SS) drafted the protocol, will contribute to drafting the final review and will check the correct use of grammar.

Chris B Del Mar (CDM) drafted the protocol and will contribute as the third review author for disagreements on clinical issues, draft the final review and check the correct use of grammar.

DECLARATIONS OF INTEREST

Respati W. Ranakusuma: none known

Yupitri Pitoyo: none known

Eka Dian Safitri: none known

Sarah Thorning: none known

Elaine M Beller: this review was supported by a grant from the NHMRC, Australia, to the Centre for Research in Evidence-Based Practice, Bond University

Sudigdo Sastroasmoro: none known

Chris B Del Mar: none known

Cochrane Library

Cochrane Database of Systematic Reviews

Systemic corticosteroids for acute otitis media in children (Review)

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB.
Systemic corticosteroids for acute otitis media in children.
Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012289.
DOI: 10.1002/14651858.CD012289.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Systemic corticosteroids for acute otitis media in children

Respati W Ranakusuma[1,2], Yupitri Pitoyo[2], Eka D Safitri[2], Sarah Thorning[3], Elaine M Beller[1], Sudigdo Sastroasmoro[2,4], Chris B Del Mar[1]

[1]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Gold Coast, Australia. [2]Clinical Epidemiology & Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital - Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia. [3]GCUH Library, Gold Coast University Hospital, Southport, Australia. [4]Department of Pediatrics, Dr. Cipto Mangunkusumo Hospital - Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

Contact address: Respati W Ranakusuma, Centre for Research in Evidence-Based Practice (CREBP), Bond University, 14 University Drive, Gold Coast, QLD, 4226, Australia. anggiranakusuma@yahoo.com, rranakus@bond.edu.au.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 3, 2018.

Citation: Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD012289. DOI: 10.1002/14651858.CD012289.pub2.

ABSTRACT

Background

Acute otitis media (AOM) is a common acute infection in children. Pain is its most prominent and distressing symptom. Antibiotics are commonly prescribed for AOM, although they have only a modest effect in reducing pain at two to three days. There is insufficient evidence for benefits of other treatment options, including systemic corticosteroids. However, systemic corticosteroids are potent anti-inflammatory drugs, and so theoretically could be effective, either alone or as an addition to antibiotics.

Objectives

To assess the effects of systemic corticosteroids (oral or parenteral), with or without antibiotics, for AOM in children.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) which contains the Cochrane ARI Group's Specialised Register, MEDLINE (Ovid), Embase (Elsevier), CINAHL (EBSCO), Web of Science (Thomson Reuters), and LILACS (BIREME) for published studies, and ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for completed and ongoing studies, to 20 February 2018. We checked the reference lists of all primary studies and review articles for additional references and contacted experts in the field to identify additional unpublished materials.

Selection criteria

We included randomised controlled trials of children with AOM that compared any systemic corticosteroid (oral or parenteral) with placebo, either with antibiotics (corticosteroid plus antibiotic versus placebo plus antibiotic) or without antibiotics (corticosteroid versus placebo).

Data collection and analysis

Three review authors (EDS, RR, YP) independently screened the titles and abstracts and retrieved the full texts of potentially relevant studies. We independently extracted study characteristics and outcome data from the included studies, and assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions.* We assessed study quality using the GRADE method.

Main results

We included two studies involving 252 children with AOM aged from three months to six years receiving hospital ambulatory care who were treated with intramuscular ceftriaxone, and who were then randomised to the corticosteroid group (corticosteroid and corticosteroid plus antihistamine) or the placebo group (antihistamine and double placebo). In one study, children also had a needle aspiration of middle ear fluid. Both studies were at unclear risk of bias for allocation concealment, and unclear to high risk of bias for selective reporting.

One study (N = 179) included pain as an outcome, but we were unable to derive the proportion of children with persistent pain at Day 5 and Day 14. Reduction of overall or specific symptoms was presented as improvement in clinical symptoms and resolution of inflamed tympanic membranes without the need for additional antibiotic treatment: at Day 5 (94% of children in the treatment group (N = 89) versus 89% in the placebo group (N = 90); risk ratio (RR) 1.06, 95% confidence interval (CI) 0.97 to 1.16) and Day 14 (91% versus 87%; RR 1.05, 95% CI 0.95 to 1.17). Low-quality evidence meant that we are uncertain of the effectiveness of corticosteroids for this outcome.

The second study (N = 73) reported a reduction of overall or specific symptoms without additional antibiotic treatment during the first two weeks as a favourable outcome. Children in the treatment group had more favourable outcomes (adjusted odds ratio 65.9, 95% CI 1.28 to 1000; P = 0.037), although the numbers were small. We were unable to pool the results with the other study because it did not report the proportion of children with this outcome by treatment group. Only one study reported adverse effects of corticosteroids (e.g. drowsiness, nappy rash), but did not quantify incidence, so we were unable to draw conclusions about adverse effects. Neither study reported a reduction in overall or specific symptom duration.

Authors' conclusions

The evidence for the effect of systemic corticosteroids on AOM is of low to very low quality, meaning the effect of systemic corticosteroids on important clinical outcomes in AOM remains uncertain. Large, high-quality studies are required to resolve the question.

PLAIN LANGUAGE SUMMARY

Systemic corticosteroids for improving symptoms in children with acute middle ear infection

Review question

We reviewed the evidence on the effects of corticosteroids given by mouth or injection for acute middle ear infection (acute otitis media (AOM)) in children, particularly in improving symptoms such as ear pain, fever, irritability, lack of sleep, and lack of appetite. We also looked at the side effects of corticosteroids.

Background

Acute otitis media is common in children and causes ear pain and non-specific symptoms such as fever, irritability, and deafness. It is often treated with antibiotics, although ear pain generally resolves within two days, and antibiotics help symptoms only slightly. Other treatments (such as over-the-counter antihistamines and decongestants) do not help very much.

Corticosteroids are often prescribed to reduce inflammation in children for other illnesses, and so may also help symptoms of AOM, which is an inflammatory process. We investigated whether using corticosteroids was better or worse than nothing in improving AOM-related symptoms.

Search date

Our evidence is current to 20 February 2018.

Study characteristics

We included two studies involving 252 children with AOM, aged from three months to six years, receiving hospital ambulatory care. Children were treated with an antibiotic injection and either oral corticosteroid or a placebo (treatment with no effect). In one study, fluid from the middle ear was collected by inserting a needle through the eardrum to measure the level of inflammation.

Study funding sources

The National Institutes of Health (NIH) and the National Center for Research Resources, NIH, US Public Health Service funded both studies. Pharmaceutical companies provided the drug but did not contribute any other scientific or financial support.

Key results and quality of evidence

Corticosteroids did not make a significant difference in improving the symptoms and inflammation of the eardrum(s) at Day 5 and Day 14, but we are unsure of this effect due to the small numbers of children in the studies. There were no significant differences between the corticosteroid and placebo groups in terms of resolving fluid in children's middle ears (at 1, 2, and 3 months) and experiencing new episodes of AOM (at 1, 2, 3 months, and 4 and 6 months). Neither study reported a reduction in the duration of overall or specific symptoms, rupture of eardrum(s), the occurrence of middle ear inflammation in the other ear following the current ear infection, or serious complications. Only one study reported the overall side effects identified during the trial (e.g. drowsiness, dry mouth, diaper rash, nervousness).

We could not draw any conclusions regarding the effects of corticosteroids for AOM in children.

The quality of evidence included in this review was low to very low due to few children included in two small studies. We are uncertain about whether or not corticosteroids are useful in relieving pain from AOM.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Systemic corticosteroids versus placebo for children with acute otitis media

Patient or population: children with acute otitis media
Setting: paediatric outpatient clinics
Intervention: systemic corticosteroids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with systemic corticosteroids				
Proportion of children with pain at various time points						
Day 5	Study population		Not estimable	(0 studies)	-	Only pre-treatment data were available. We could not retrieve post-treatment data
	0 per 1000	0 per 1000 (0 to 0)				
Day 14	Study population		Not estimable	(0 studies)	-	Only pre-treatment data were available. We could not retrieve post-treatment data
	0 per 1000	0 per 1000 (0 to 0)				
Reduction of overall or specific symptoms at various time points						
Day 5	Study population		RR 1.06 (0.97 to 1.16)	179 (1 RCT)	⊕⊕◯◯ LOW [1]	This outcome was represented as the proportion of children for whom symptoms and inflamed eardrum(s) resolved and who did not require additional antibiotic treatment

	889 per 1000	942 per 1000 (862 to 1000)				
Day 14	Study population		RR 1.05 (0.95 to 1.17)	179 (1 RCT)	⊕⊕◯◯ LOW [1]	This outcome was represented as the proportion of children for whom symptoms and inflamed eardrum(s) resolved and who did not require additional antibiotic treatment
	867 per 1000	910 per 1000 (823 to 1000)				
Reduction in overall or specific symptom duration	Study population		Not estimable	(0 studies)	-	No study provided data for this outcome.
	0 per 1000	0 per 1000 (0 to 0)				
Adverse effects	Study population		Not estimable	(0 studies)	-	The available data were reported as an overall result. We could not retrieve data from each individual group (overall side effects across all groups: drowsiness (22% to 34%), dry mouth (16% to 27%), increased urine amount (14% to 27%), nappy rash (7% to 32%), nervousness (7% to 20%), and decreased urine amount (0% to 11%)).
	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to study limitations (unclear description of the allocation concealment and evidence of selective reporting) and one level due to indirectness (differences between the outcome of interest (i.e. in reporting, measurements) and reported outcomes).

BACKGROUND

Description of the condition

Acute otitis media (AOM) is a common complication of acute respiratory infections. A prospective, longitudinal cohort study found an overall incidence of 37% over one year for AOM following an acute respiratory infection usually caused by viruses, in children aged six months to three years (Chonmaitree 2008). Before the age of three years, approximately 80% of children experience at least one episode of AOM, mostly affecting those younger than two years old (Lieberthal 2013; SACHCN 2014; Vergison 2010). Immaturity and the anatomy of the Eustachian tube may contribute to AOM (SACHCN 2014).

Clinicians commonly diagnose AOM in children who present with ear pain (holding, tugging, rubbing of the ear in a non-verbal child) or intense erythema of the tympanic membrane, or moderate-to-severe bulging of the tympanic membrane, or ear discharge not from otitis externa (NSW Health 2014; Pichichero 2015).

Acute symptoms (pain and systemic symptoms) resolve in 60% of children within 24 hours and 80% within 72 hours (Morris 2009; Venekamp 2015). Children aged up to two years often experience more severe and protracted illness (Chonmaitree 2008). Studies have reported that 62% of children aged up to 12 months experience at least one episode of AOM. Acute otitis media is recurrent in 10% to 30%, and 2% to 25% of children experience persistent middle ear effusion for three months, which may require ventilation tube (grommet) insertion to relieve the accompanying deafness (Gribben 2012; Kitamura 2015).

The prevalence of AOM varies across Asian countries. In Korea, a 1991 national survey reported a point prevalence of 0.08% for AOM in children aged up to 15 years (Lee 2012); in Malaysia, 9% of children aged three months to 12 years experienced AOM over the previous three years (Tikaram 2012). A 2005 study in Taiwan found that 13.2% of children aged up to seven years had experienced AOM (Ting 2012). In East Jakarta, Indonesia, the point prevalence of AOM in children aged less than 18 years was 5.4% (Umar 2013).

The risk of AOM is high in Australian indigenous populations: a cluster survey in Indigenous versus non-Indigenous children found that severe otitis media was more prevalent in Indigenous children (7.9%) compared to non-Indigenous children (1.7%) (Gunasekera 2007).

Pain is the most common symptom of AOM. Guidelines recommend analgesics such as paracetamol or ibuprofen (Lieberthal 2013; NSW Health 2014; SACHCN 2014). Analgesics have been trialed against placebo in AOM, with ibuprofen (7% versus 25.3%; risk ratio (RR) 0.28, 95% confidence interval (CI) 0.11 to 0.71) and paracetamol (9% versus 25.3%; RR 0.38, 95% CI 0.17 to 0.85) both significantly reducing ear pain 48 hours after treatment (Bertin 1996; Bradley-Stevenson 2007). However, there is insufficient evidence of efficacy for topical analgesics reducing ear pain in AOM (Foxlee 2011).

Antibiotics are also commonly prescribed in the treatment of AOM. Antibiotics have a modest effect in reducing pain at two to three days, with a number needed to treat for an additional beneficial outcome (NNTB) of 20 children (Venekamp 2015), and yet 11% to 19% of children still experience symptoms to Day 6 (Chonmaitree 2003; Lieberthal 2013). Antibiotics have no effect on deafness caused by middle ear effusion, which persists in 30% to 60% of children one month following AOM, and three months in 15% to 25% (Chonmaitree 2003).

Recurrent AOM after an initial attack is common, with about one-third of children experiencing recurrence within a month (Chonmaitree 2003).

Antibiotics are not considered mandatory. An alternative strategy is observation (Lieberthal 2013; Pichichero 2015).

There is limited evidence for the use of decongestant/antihistamine combinations for AOM in children: a Cochrane Review found a small statistical benefit from the combination medication, but the clinical significance was minimal and the contributing studies may have been biased (Coleman 2008).

Description of the intervention

Corticosteroids are natural steroid hormones produced by the adrenal cortex, which can be synthetically manufactured. Corticosteroids have many physiological effects, including an anti-inflammatory role (Gupta 2008), which is exploited for many acute and chronic inflammatory illnesses in adults and children (Coutinho 2011).

How the intervention might work

The pathophysiology of AOM is complex. However, inflammation is an important mechanism. This mechanism is induced by both cellular and chemical mediators, such as cytokines, chemokines, mast cells, prostaglandins, and leukotrienes (Juhn 2008). Corticosteroids could act by suppressing inflammation. Corticosteroids are effective in some other acute respiratory infections, for example when combined with antibiotics for sore throat (Hayward 2012), acute sinusitis (Venekamp 2014), and acute bacterial meningitis (Brouwer 2015). A Cochrane Review on the use of topical intranasal steroids for otitis media effusion in children found no evidence of benefit in terms of symptom relief (including ear symptoms that are crucial in the management of AOM) either at short- or longer-term follow-up (Simpson 2011).

Several studies have investigated corticosteroids for chronic otitis media with effusion (OME). A Cochrane Review on the use of topical intranasal steroids for OME in children found no evidence of benefit in improving ear symptoms, either at short- or longer-term follow-up (Simpson 2011). However, a recent randomised

controlled trial on the use of oral steroids, with and without intranasal steroids, compared to watchful waiting in children with OME demonstrated that fewer children had incomplete resolution or persistent middle ear effusion, or both, with corticosteroids compared with the watchful-waiting group at six weeks after treatment, but not in the longer term (three to nine months) (Hussein 2017). These findings demonstrate that corticosteroids may work for middle ear inflammation.

There are theoretical risks associated with corticosteroids, especially with long-term use, including Addisonian crisis after stopping treatment abruptly. However, short-term use (≤ 1 week) has not been found to cause adverse effects, nor require dose-tapering (Chonmaitree 2003; Deshmukh 2007; Venekamp 2014).

Why it is important to do this review

Antibiotics for treating AOM in children are weakly effective, but are used very often in the absence of a more effective treatment. Treatment with antibiotics also risks antibiotic resistance. Alternative, more effective treatments are therefore needed. Systemic corticosteroids may fill that role, either as a monotherapy or in addition to antibiotics. However, there is insufficient evidence to support corticosteroid treatment for AOM (Principi 2013). A Cochrane Review is important to assess studies that have not been systematically reviewed.

OBJECTIVES

To assess the effects of systemic corticosteroids (oral or parenteral), with and without antibiotics, for AOM in children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included children aged up to 15 years with AOM (this upper age being the limit for adolescence) (UNICEF 2011).

We defined AOM as "...the rapid onset of ear pain accompanied with bulging and/or hyperaemic tympanic membrane and the presentation of middle ear effusion" (Lieberthal 2013; Pichichero 2015). We included both unilateral and bilateral AOM. We included children from all recruitment settings.

We excluded children with contraindications to corticosteroid therapy (e.g. immunodeficient or immunocompromised); children with anatomic or physiological disorders of the ear (including those with ventilation tubes, because this procedure is principally used for non-acute (chronic) otitis media with effusion) or nasopharynx; and those with chronic middle ear effusion.

Types of interventions

We included studies that compared any type of systemic corticosteroid (e.g. oral or parenteral) with placebo, either without antibiotics (i.e. corticosteroid versus placebo) or with antibiotics (i.e. corticosteroid plus antibiotic versus placebo plus antibiotic).

We excluded studies using topical corticosteroid such as intranasal spray.

Participants could have used paracetamol as an antipyretic analgesic (Bertin 1996).

Types of outcome measures

Primary outcomes

1. Proportion of children with pain at various time points (24 hours; 2 to 3 days; and 4 to 7 days (time points taken from Venekamp 2015)).
2. Reduction of overall or specific symptoms (e.g. ear discomfort, hearing loss, irritability, sleep disturbance, diminished appetite). Reduction of overall or specific symptoms may have been measured using visual analogue scales or validated symptom scales specific to otitis media such as the Acute Otitis Media Severity of Symptoms Scale (AOM-SOS), Otitis Media Outcome-22 questionnaire (OMO-22), Otitis Media-6 quality of life survey (OM-6), or others (Timmerman 2007).
3. Reduction in overall or specific symptom duration.
4. Adverse effects.

Secondary outcomes

1. Changes in tympanometry measurements at various time points as an objective assessment of the resolution of AOM (e.g. middle ear pressure, tympanogram curve types).
2. Tympanic membrane perforation. This is considered to be a mild complication of AOM (Principi 2017), usually spontaneously healing in a few days (four to six days) (Principi 2017; Slovik 2008).
3. Contralateral otitis (in children with unilateral infection).
4. AOM recurrence, which was defined as the occurrence of AOM episodes within one month after completion of antibiotic therapy (Pichichero 2000).
5. Serious complications related to AOM such as mastoiditis and meningitis.

Search methods for identification of studies

Electronic searches

We searched the following databases up to 20 February 2018:

- Cochrane Central Register of Controlled Trials, which contains the Cochrane ARI Group's Specialised Register, (CENTRAL; Issue 1, 2018, in the Cochrane Library) using the strategy in Appendix 1;
- MEDLINE via Ovid (from 1946 to 20 February 2018) using the strategy in Appendix 2;
- EMBASE via Elsevier (from 1974 to 20 February 2018) using the strategy in Appendix 3;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) via EBSCO (from 1981 to 20 February 2018) using the strategy in Appendix 4;
- Web of Science via Thomson Reuters (from 1900 to 20 February 2018) using the strategy in Appendix 5; and
- LILACS (Latin American and Caribbean Literature in Health Sciences) via BIREME (from 1985 to 20 February 2018) using the strategy in Appendix 6.

We searched the following trials registries on 20 February 2018:

- ClinicalTrials.gov (www.clinicaltrials.gov); and
- the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

We did not restrict results by language or publication status (published, unpublished, in press, or in progress).

We combined the MEDLINE (Ovid) search strategy (Appendix 2) with the Cochrane Highly Sensitive Search Strategy to identify randomised trials in MEDLINE: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011). We adapted these search terms to search other databases (Embase, CENTRAL, CINAHL, Web of Science and LILACS). We planned to assess whether we would need to apply a filter for retrieving studies in children (Boluyt 2008). (This was not required because searches identified relatively few records). We imposed no language or publication restrictions.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We contacted experts in the field to identify additional unpublished materials.

Data collection and analysis

Selection of studies

Three review authors (EDS, RR, YP) independently screened the titles and abstracts of all studies identified by the searches. We retrieved full-text study reports of potentially relevant studies. Three review authors (EDS, RR, YP) independently screened the retrieved reports to identify studies for inclusion, and the reasons for exclusion of ineligible studies were recorded. Any disagreements were resolved through discussion and consulting with a fourth review author (EMB). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was assessed in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2010).

Data extraction and management

We used a data collection form that had been piloted to collate study characteristics and outcome data. Three review authors (EDS, RR, YP) independently extracted study characteristics from the included studies. We extracted the following study characteristics:

1. methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study;
2. participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria;
3. interventions: intervention, comparison, concomitant medications, and excluded medications;
4. outcomes: primary and secondary outcomes specified and collected, and time points reported; and
5. notes: funding for the trial and notable conflicts of interest of trial authors.

We noted if outcome data were not reported in a usable way in the Characteristics of included studies table. Any disagreements were resolved by consensus. A review author (RR) entered data into Review Manager 5 (Review Manager 2014). We double-checked that data were entered correctly by comparing data presented in the systematic review with the study reports. Two review authors (EDS, YP) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Three review authors (EDS, RR, YP) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion with another review author (EMB). We assessed the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;

5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

We took into account the risk of bias for the studies that contributed to that outcome when considering treatment effects.

Measures of treatment effect

We entered outcome data for each study into data tables in Review Manager 5 to calculate the treatment effects (Review Manager 2014). We intended to use the risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and the mean difference (MD) or standardised mean difference (SMD) for continuous outcomes. Because several outcomes were incompletely reported or unavailable for pooling, we did not undertake meta-analysis. Nonetheless, we used RR with 95% CI in reporting both our primary and secondary outcomes reported by one study (i.e. the proportion of children with pain, reduction of overall or specific symptoms, changes in tympanometry measurements, and AOM recurrence at various time points).

Unit of analysis issues

We did not expect any trials to have applied cross-over or cluster-randomised designs.

For studies with more than two intervention groups, where more than two groups were eligible for our review, we planned to follow the methods in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), that is in studies with more than one control group or more than one intervention group, we would combine the results of the control or intervention groups, respectively.

Dealing with missing data

We contacted trial authors to verify key study characteristics and to obtain missing numerical outcome data (i.e. numbers of children in each group for several outcomes). However, the trial authors were unable to provide these data.

We were unable to locate missing numerical outcome data such as standard deviations or correlation coefficients. We thus did not calculate the missing parameters from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not impute values (e.g. correlation coefficients), therefore we did not perform sensitivity analyses to assess how sensitive the results were to reasonable changes in the assumptions that were made in the imputation.

Assessment of heterogeneity

We planned to use the Chi² test and I² statistic to measure heterogeneity among the studies in each analysis. If we identified substantial heterogeneity (over 50% as specified in the *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011), we would report this and explore the possible causes by conducting prespecified subgroup analysis. We were aware that when there are few studies in a meta-analysis there is uncertainty in the I² statistic measurement. In such case, we planned to use a P value of 0.10 rather than 0.05 in the Chi² test to determine statistical heterogeneity (Higgins 2011). However, due to insufficient numbers of studies and available outcome data, we were unable to pool the included studies and assess their heterogeneity.

Assessment of reporting biases

We had planned to use funnel plots to explore possible small-study and publication biases if we were able to pool more than 10 trials. However, the small number of included studies precluded this.

Data synthesis

We had planned to pool data from studies that we judged to be clinically homogeneous using Review Manager 5 (Review Manager 2014), employing a fixed-effect model. If a single true effect was not plausible due to variation in populations and interventions or substantial heterogeneity, we would use a random-effects model instead (DerSimonian and Laird method) (Higgins 2011). If more than one study provided usable data in any single comparison, we would perform a meta-analysis. However, we could not do so because there were only includable data from one study.

GRADE and 'Summary of findings' table

We had planned to create a 'Summary of findings' table using the following primary outcomes: proportion of children with pain at various time points (24 hours; 2 to 3 days; 4 to 7 days); reduction of overall or specific symptoms; reduction in overall or specific symptom duration; and adverse effects of corticosteroids. However, due to insufficient available outcome data, we were only able to report one primary outcome, that is reduction of overall or specific symptoms.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004; GRADE 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins

2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We justified all decisions to downgrade or upgrade the quality of studies using footnotes and made comments to aid readers' understanding of the review.

Subgroup analysis and investigation of heterogeneity

We had planned to carry out the following subgroup analyses using the Chi² test to test for subgroup interactions (Review Manager 2014):

1. short- versus long-term use of corticosteroids (≤ 1 week versus > 1 week);
2. type of corticosteroids (i.e. prednisolone, dexamethasone, etc.); and
3. corticosteroids as monotherapy versus adjuvant to antibiotics.

However, the small number of included studies precluded this.

Sensitivity analysis

We had planned to carry out sensitivity analyses by identifying and excluding studies with high risk of bias or low methodological quality based on the Cochrane 'Risk of bias' assessment. However, the small number of included studies precluded this.

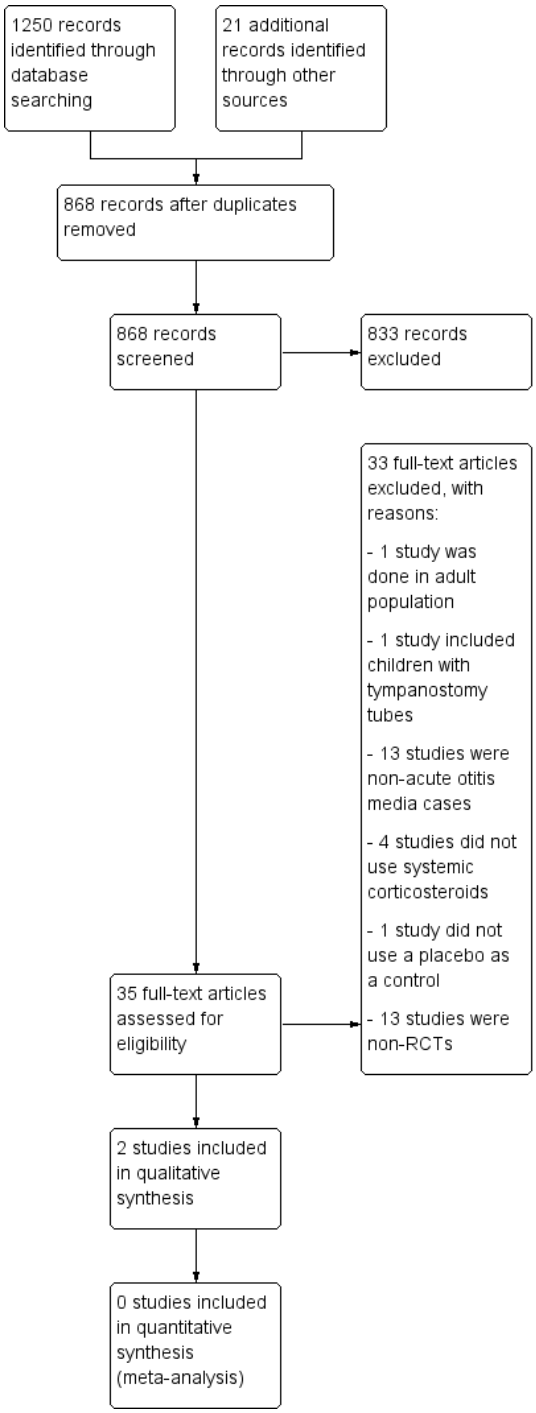
RESULTS

Description of studies

Results of the search

We retrieved 1250 records from electronic databases and 21 records from clinical trial registry searches (Figure 1). After removing duplicates, three review authors (EDS, RR, YP) independently assessed 868 records based on titles and abstracts, and then reviewed the full-text reports. After reviewing the full-text reports based on the eligibility criteria, we identified 35 articles. We excluded 33 articles: one included only adults (Arusgamov 1966); one included children with tympanostomy tubes (Ruohola 1999); 13 included chronic otitis media (Califano 2014; Chinski 2003; Choung 2008; Daly 1991; Endo 1997; Hearey 1990; Hussein 2017; Persico 1978; Puhakka 1985; Saffar 2001; Schwartz 1979; Schwartz 1981; Woodhead 1986); four included non-systemic corticosteroids (Cajgfinger 1967; Chirileanu 1978; Martin 1975; Terjung 1967); 13 included non-RCTs (Albernaz 2001; Capella 1984; Carvalho 1984; Crysdale 1984; Fradis 1983; Han 2009; Matsubara 2007; Oppenheimer 1968; Pulkki 2006; Rosenfeld 1992; Roydhouse 1978; Seehusen 2012; Sergienko 1975); and one did not include a placebo (Wang 2007).

Figure 1. Study flow diagram.



We included two studies in the review (Chonmaitree 2003; McCormick 2003).

Included studies

We included two studies with a total of 252 children with AOM (Chonmaitree 2003; McCormick 2003). We contacted both trial authors and obtained additional information regarding the randomisation and allocation concealment procedures, and the blinding of the outcome assessors for these two studies. Methods, participants, interventions, and outcomes of the included studies are presented in the Characteristics of included studies table.

Design

Chonmaitree 2003 and McCormick 2003 were 2 x 2 factorial, double-blind, randomised, placebo-controlled trials.

Participants and settings

Chonmaitree 2003 and McCormick 2003 included 198 and 80 children, respectively, aged from three months to six years with AOM. Both studies analysed children who had at least 70% adherence to the treatment measured by diary entries, weight of medicine bottles, and the availability of outcome data on the second visit and subsequent other visits. Chonmaitree 2003 analysed 179 of 198 children, and McCormick 2003 analysed 73 of 80 children due to their adherence to the trial. We therefore analysed these studies based on available cases instead of intention-to-treat. The two studies had similar exclusion criteria. Children were excluded if they had:

- anatomic or physiologic ear and/or nasopharyngeal defects;
- major medical or immunology disorders;
- current treatment with other medication;
- antibiotic use in the previous week;
- history of allergy to cephalosporin drugs;
- tympanostomy tube or perforated tympanic membrane;
- previous exposure to chickenpox in preceding three weeks.

Both studies were conducted at the paediatric outpatient clinic of the University of Texas Medical Branch at Galveston, USA.
The main difference between the studies was that McCormick 2003 performed tympanocentesis to measure the level of histamine and leukotriene B (LTB4) in the middle ear in all children, whereas Chonmaitree 2003 did not. Because all children in McCormick 2003 underwent tympanocentesis, any confounding effect of this procedure was eliminated. However, the potential pain relief effect of tympanocentesis, which might modify outcomes for both groups, made McCormick 2003 more difficult to generalise.

Interventions and comparators

Children in both Chonmaitree 2003 and McCormick 2003 were randomly allocated to one of four groups:

1. corticosteroid (prednisolone 2 mg/kg/day) and placebo;
2. antihistamine (chlorpheniramine maleate 0.35 mg/kg/day) and placebo;
3. corticosteroid plus antihistamine;
4. two placebos of corticosteroid and antihistamine.

All medicines were given in three divided doses for five days, including the placebos, which were matched with prednisolone and chlorpheniramine maleate for their colour and taste. Following the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we therefore combined the results of these groups into corticosteroid group (corticosteroid and the combination of corticosteroid and antihistamine groups) and placebo group (antihistamine and double placebo groups). All children in these studies received a single-dose antibiotic intramuscular injection of ceftriaxone (50 mg/kg) at the baseline visits.

Outcomes

Chonmaitree 2003 reported the main outcomes as:

1. the rate of treatment failure during the first two weeks (Day 5 and Day 14);
2. duration of middle ear effusion (1, 2, and 3 months); and
3. rate of recurrence of AOM (at 1, 2, 3, and 4 to 6 months).

Treatment failure was defined as the persistence of any clinical symptom(s) and the inflammation of tympanic membrane requiring antibiotic treatment. Chonmaitree 2003 also reported the reduction of symptoms and signs severity score during the first two weeks, persistent middle ear effusion measured using pneumatic otoscope and tympanometry during the first three months, and the side effects (i.e. drowsiness, dry mouth, excitability, diaper rash, increased or decreased urine amount) measured using symptom diaries. Recorded symptoms consisted of nine clinical symptoms that were scored ranging from zero (no symptom), one (mild symptom) to two (severe symptom). The symptoms were: fever (> 38 °C rectally), ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, and watery eyes. The severity of the signs was measured and scored based on the otoscopic examination of three characteristics of the tympanic membrane: position, colour/transparency, and mobility of the tympanic membrane. Each sign was scored ranging from zero (normal, shiny) to two (bulging, red/yellow, immobile) with a maximum score of six. McCormick 2003 assessed:

1. clinical outcome (improvement or failure) at visit 2 (Day 4 to Day 6) and visit 3 (Day 14) and bacterial outcome at visit 2;
2. the changes of histamine and leukotriene B4 (LTB4) of the middle ear fluid taken by tympanocentesis at the baseline and

visit 2 (Day 4 to Day 6);

3. the duration of middle ear effusion; and
4. AOM recurrence during the first four months.

Clinical improvement was defined as an improvement in clinical symptoms, clinical signs (reduced/absent of redness and bulging of tympanic membrane), and no drainage of middle ear fluid. Clinical failure was defined as persistent clinical symptoms and signs indicated by redness and bulging of tympanic membrane, purulent drainage of middle ear, with or without a positive bacterial culture. Bacterial failure was defined as the persistence of pathogen bacterial from middle ear fluid collected at visit 2 and the requirement of another cycle of antibiotic treatment. Children were considered to have a satisfactory or favourable total outcome if they experienced clinical improvement at visit 2 and visit 3 without bacterial failure and did not require antibiotic treatment during the first two weeks.

Funding sources

Both Chonmaitree 2003 and McCormick 2003 were funded by National Institutes of Health (NIH) Grant R01 DC 2620 and National Center for Research Resources, NIH, US Public Health Service (USPHS) Grant M01 RR 00073. The prednisolone oral liquid was supplied by Fisons Pharmaceuticals, Rochester, NY, and the chlorpheniramine maleate was supplied by Schering-Plough, Kenilworth, NJ. There was no other scientific or financial contribution from these pharmaceutical companies.

Excluded studies

We excluded 33 studies (Characteristics of excluded studies):

- one included only adults (Arusgamov 1966);
- one included children with tympanostomy tubes (Ruohola 1999);
- 13 included chronic otitis media (Califano 2014; Chinski 2003; Choung 2008; Daly 1991; Endo 1997; Hearey 1990; Hussein 2017; Persico 1978; Puhakka 1985; Saffar 2001; Schwartz 1979; Schwartz 1981; Woodhead 1986);
- four included non-systemic corticosteroids (Cajgfinger 1967; Chirileanu 1978; Martin 1975; Terjung 1967);
- one did not include a placebo (Wang 2007);
- 13 included non-RCTs (Albernaz 2001; Capella 1984; Carvalho 1984; Crysdale 1984; Fradis 1983; Han 2009; Matsubara 2007; Oppenheimer 1968; Pulkki 2006; Rosenfeld 1992; Roydhouse 1978; Seehusen 2012; Sergienko 1975).

Risk of bias in included studies

Overall, the risk of bias in the included studies was unclear to high (see Figure 2 and Figure 3). The two concerning biases were: 1) unclear description of allocation concealment, and 2) unclear to high risk of selective reporting due to insufficient information provided in published papers and clinical trial registries and unavailability of the trial protocols. McCormick 2003 reported the favourable total outcomes during the first two weeks as a P value, adjusted odds ratio, and 95% confidence intervals, and not as the proportion of children who had favourable or unfavourable total outcome by their treatment groups (Characteristics of included studies). However, both studies had unclear to high risk of bias for other domains, and we therefore assessed both studies at high risk of bias overall (Chonmaitree 2003; McCormick 2003).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

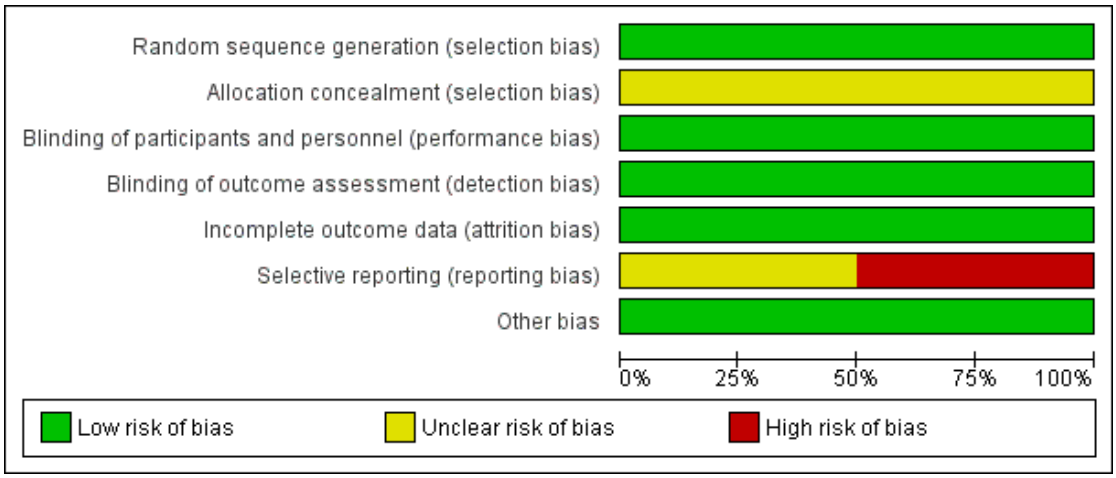
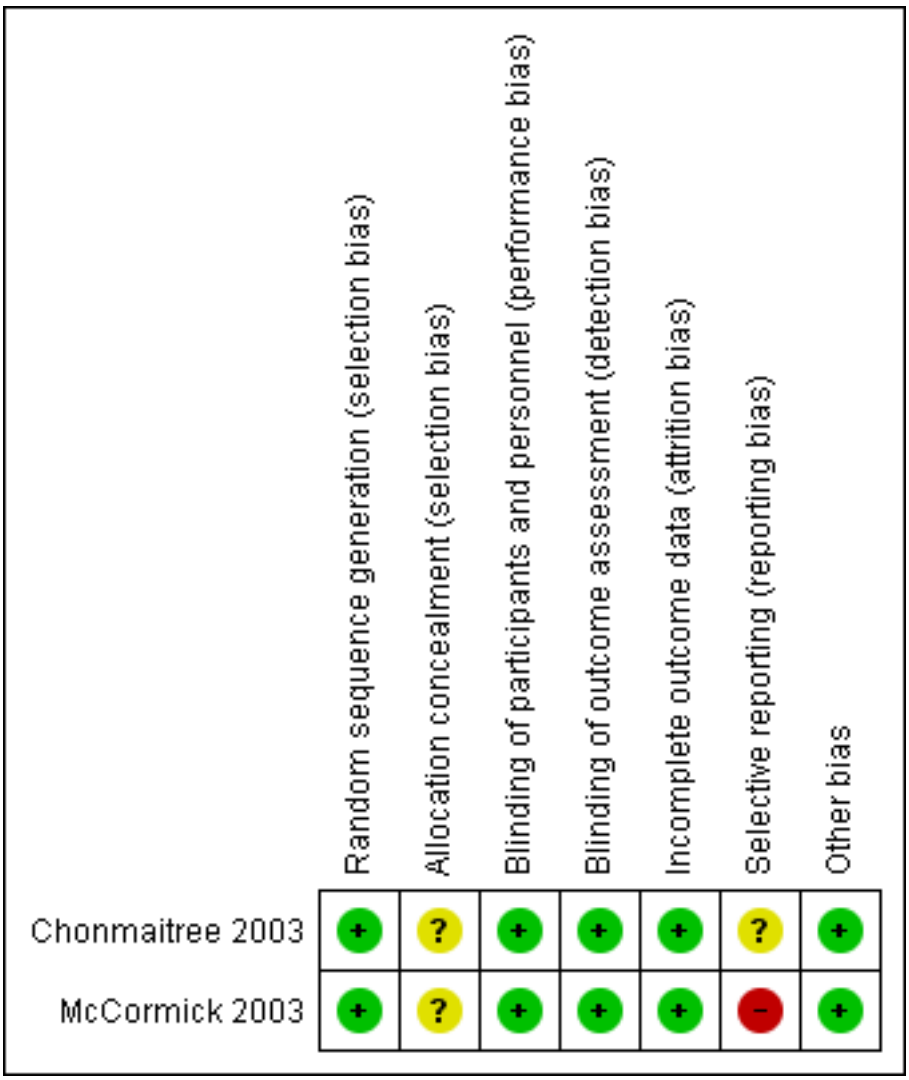


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Neither study clearly described the randomisation process and the allocation concealment. We contacted the trial authors and were informed that the randomisation in both studies used computer-generated block randomisation. There was no clear description regarding allocation concealment. Based on information provided by the trial author, only the statistician who generated the randomisation schedule knew the code, but it is unclear whether this was a group code or individual codes. We therefore assessed both studies as at unclear risk of bias for allocation concealment (Chonmaitree 2003; McCormick 2003).

Blinding

In Chonmaitree 2003 and McCormick 2003, the parents/caregivers and the examining clinicians were unaware of the type of treatment allocation. Furthermore, placebos for both corticosteroid and antihistamine were prepared similarly to the active medicine based on colour and taste. This blinding method also prevented the children and their parents/caregivers from being aware of the treatment that they had received. This information was not provided in the papers, and was obtained by contacting the trial authors. We therefore graded this as low risk for performance bias and detection bias (blinding of participants, personnel, and

outcome assessors).

Incomplete outcome data

In Chonmaitree 2003, of 198 children who were enrolled and randomised, 179 children (90.4%) were analysed for the outcomes; in McCormick 2003, of 80 children, 73 children (91.2%) were analysed for the outcomes. The requirement for being included in final analyses was at least 70% adherence to the treatment measured by the diary, the weight of medicine bottles, and the availability of the outcome data on the second visit and after. Based on the low rate of missing outcome data due to non-compliance to the study (< 10%), which was found to be mostly even in each treatment group, we graded this as low risk for attrition bias or incomplete outcome data.

Selective reporting

We were unable to retrieve the protocols for either study. Although both were registered on a clinical trial registry, there was no information regarding the primary or the secondary outcomes for both studies. In addition, McCormick 2003 did not provide the results of clinical outcome at visit 2 and visit 3. We therefore judged Chonmaitree 2003 as at unclear risk and McCormick 2003 as at high risk for reporting bias or selective reporting.

Other potential sources of bias

We identified no other potential sources of bias. We contacted the trial authors (Chonmaitree 2003; McCormick 2003), who declared that there was no scientific or financial contribution from the pharmaceutical industry. We therefore judged this domain as at low risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Systemic corticosteroids compared to placebo for children with acute otitis media

Primary outcomes

1. Proportion of children with pain at various time points

Chonmaitree 2003 recorded pain as one of nine clinical symptoms. However, the trial authors only reported the proportion of children with pain before treatment (at the baseline visit) and not the proportion of children with pain after treatment. We contacted the trial authors but they could not provide the data (the study was conducted 15 years ago).

2. Reduction of overall or specific symptoms

Chonmaitree 2003 recorded nine clinical symptoms: fever > 38 °C rectally, ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, and watery eyes, based on three grading scores. The author only reported the proportion of children with pre-treatment symptoms in each group. The post-treatment symptoms were reported as overall results of reduction in symptom severity score and otoscopic sign scores. There were no significant differences between groups at each follow-up visit. We contacted the trial authors but they could not provide the data.

Chonmaitree 2003 reported clinical failure as a main outcome at various time points: visit 2 (Day 5) and visit 3 (Day 14). We converted the outcome to clinical improvement in order to represent the reduction of overall or specific symptoms. At visit 2, there were 84 children in the corticosteroid group (N = 89) compared to 80 children in the placebo group (N = 90) with improvement of clinical symptom(s) and otoscopic signs of AOM (94% versus 89%; risk ratio (RR) 1.06, 95% confidence interval (CI) 0.97 to 1.16), whilst at visit 3, there were 81 children in the corticosteroid group compared to 78 children in the placebo group (91% versus 87%; RR 1.05, 95% CI 0.95 to 1.17; Analysis 1.1). Although these results reflected the benefit of corticosteroids, there were no statistically significant differences between the two groups at these time points.

McCormick 2003 defined favourable total outcome as the improvement of clinical outcomes (e.g. reduced or absence of tympanic membrane inflammation, no ear discharge) at visit 2 (Day 4 to Day 6) and visit 3 (Day 14) without bacterial finding in the middle ear fluid at visit 2, without the need for additional antibiotic treatment during the first two weeks. The favourable total outcome was more likely to be found in the corticosteroid group compared to other groups (adjusted odds ratio 65.9, 95% CI 1.28 to 1000; P = 0.037). As the trial author did not report the proportion of children who had favourable total outcome in the other groups (i.e. corticosteroid plus antihistamine group, corticosteroid plus placebo group, antihistamine plus placebo group, double placebo group), we could not pool the data from this study with Chonmaitree 2003.

We rated the evidence from these studies as low quality due to serious risk of bias (unclear description of the allocation concealment) and indirect results, which was caused by the difference between the outcome of interest (i.e. reduction of overall or specific symptoms) and the outcomes reported (i.e. combination of persistent clinical symptom(s) and signs of inflammation of the tympanic membrane(s) that required another cycle of antibiotic treatment) (Summary of findings for the main comparison). Systemic corticosteroids may therefore make little or no difference to clinical outcomes.

3. Reduction in overall or specific symptom duration

Neither included trial reported the reduction in overall or specific symptom duration.

4. Adverse effects

Chonmaitree 2003 recorded unfavourable effects in symptom diaries daily. However, the trial authors reported adverse effects as overall side effects across all groups: drowsiness (22% to 34%), dry mouth (16% to 27%), increased urine amount (14% to 27%), nappy rash (7% to 32%), nervousness (7% to 20%), and decreased urine amount (0% to 11%). No correlation was reported between the use of corticosteroid and the risk of viral infection by comparing the persistence and the occurrence of new viral infections in the two weeks following the baseline visit. We contacted the trial authors, but outcome data by individual group were not available.

Secondary outcomes

1. Changes in tympanometry measurements at various time points

Chonmaitree 2003 represented changes in tympanometry measurement at various time points as the proportion of children with persistent middle ear effusion measured by pneumatic otoscope and tympanometry. We converted this to the proportion of children who had resolution of middle ear effusion. Resolution of middle ear effusion was reported at three different time points as follows: at one month, 45 children in the corticosteroid group (N = 89) versus 38 children in the placebo group (N = 90) (50% versus 42%; RR 1.20, 95% CI 0.87 to 1.64); at two months, 62 versus 52 children in the corticosteroid and placebo groups, respectively (70% versus 58%; RR 1.21, 95% CI 0.96 to 1.51); and at three months, 61 versus 61 children in the corticosteroid and placebo groups, respectively (76% versus 68%; RR 1.13, 95% CI 0.94 to 1.35; Analysis 1.2). None of these results showed statistically significant differences between the two groups. McCormick 2003 did not report this outcome.

We rated this evidence as very low quality due to serious risk of bias from unclear allocation concealment; imprecision because the CI included both the possibility of resolution and persistent middle ear effusion during these time points; and indirect results due to the difference between the outcome of interest (i.e. changes in tympanometry measurements) and those reported (i.e. proportion of children with persistent middle ear effusion). It therefore remains uncertain whether systemic corticosteroids improve middle ear effusion.

2. Tympanic membrane perforation

Neither included trial reported tympanic membrane perforation.

3. Contralateral otitis (in children with unilateral infection)

Neither included trial reported contralateral otitis.

4. AOM recurrence

Chonmaitree 2003 reported recurrence cumulatively during the six-month period of follow-up: at one month, there were 15 children in the corticosteroid group versus 12 children in the placebo group with recurrence of AOM (17% versus 13%; RR 1.26, 95% CI 0.63 to 2.55); at two months, 20 versus 24 children in corticosteroid and placebo groups, respectively (22% versus 27%; RR 0.84, 95% CI 0.50 to 1.41); at three months, 19 versus 29 children in corticosteroid and placebo groups, respectively (21% versus 32%; RR 0.66, 95% CI 0.40 to 1.09); and at four to six months, 33 and 36 children in corticosteroid and placebo groups, respectively (37% versus 40%; RR 0.93, 95% CI 0.64 to 1.34; Analysis 1.3).

McCormick 2003 reported that there were no statistically significant differences in terms of AOM recurrence at the first or fourth month between the groups.

We rated this evidence as low quality due to serious risk of bias from unclear allocation concealment and imprecise results. The wide CIs may include favourable and unfavourable effects of corticosteroids on AOM recurrence. It is therefore uncertain whether corticosteroids improve or reduce the recurrence of AOM.

5. Serious complications

Neither included trial reported serious complications.

DISCUSSION

Summary of main results

We included two small randomised, double-blind, placebo-controlled studies with a total of 252 participants (Chonmaitree 2003; McCormick 2003). Low- to very low-quality evidence demonstrated that corticosteroids did not make a significant difference in improving clinical outcomes (e.g. symptoms, inflammation of the eardrum), resolution of middle ear effusion, and AOM recurrence. However, we are uncertain of these results due to wide confidence intervals around the estimates.

Although McCormick 2003 reported a significant difference between the children in the corticosteroid and placebo groups who had clinical improvement during the first two weeks, we were unable to meta-analyse the results due to insufficient information from the published paper and incompleteness of outcome reporting. This study also reported that there was no significant difference between corticosteroid and placebo groups in AOM recurrence at the first or fourth month.

Adverse effects, as one of our primary outcomes, was reported by Chonmaitree 2003 as an overall result (i.e. drowsiness, nervousness, dry mouth, diaper rash, increased and decreased urine amount) but not by treatment group. Neither of the included studies reported reduction of overall or specific symptom duration, tympanic membrane perforation, contralateral otitis, or serious complications related to AOM.

Overall completeness and applicability of evidence

All participating children in both studies received antibiotics at their baseline visits; this was because only children with high-risk AOM were included in Chonmaitree 2003, but no reason was provided for McCormick 2003. These results are therefore best generalised to children with high-risk AOM.

Pain is one of the most common symptoms of AOM and is distressing for both children and their parents. Although for more than 50% of children with AOM, symptoms resolve within 24 hours with or without antibiotic treatment, almost one-fifth of children with AOM treated with antibiotics have symptoms that persist for up to six days (Chonmaitree 2003; Venekamp 2015). To date, physicians tend to prescribe medication for AOM to relieve pain and other distressing symptoms, including antibiotics, despite the self limiting nature of AOM. Antibiotics are still commonly prescribed for AOM, although evidence demonstrates that they are most likely beneficial for severe cases (i.e. fever $\geq$ 39 ºC, moderate to severe ear pain), bilateral AOM in young children, or AOM with perforated tympanic membrane(s) (Lieberthal 2013; NSW Health 2014; Venekamp 2015). Due to the modest benefits of antibiotics and their potential side effects and risk of antibiotic resistance (Venekamp 2015), alternative treatment for AOM, such as corticosteroids as an anti-inflammatory medication, could improve clinical symptoms of AOM, particularly pain. The proportion of children with pain (a primary outcome of this review) was evaluated by Chonmaitree 2003. However, this outcome was only reported before treatment, therefore we could not assess the effect of corticosteroids in improving pain alone.

Aside from the beneficial effects of corticosteroids on clinical outcomes, assessing adverse effect or harm is also very important. Unfortunately, we could not assess data for this outcome due to incomplete outcome reporting (Chonmaitree 2003).

This review demonstrated insufficient and low- to very low-quality evidence for the effects of systemic corticosteroids. We are uncertain whether corticosteroids improve important clinical outcomes of AOM (i.e. pain and overall symptoms, middle ear effusion, AOM recurrence) due to the small number of included studies. Consequently, the overall completeness and applicability of evidence is very low.

Quality of the evidence

We judged the evidence as low to very low quality.

We downgraded the quality of the evidence to low for the primary outcomes due to serious risk of bias and indirectness of the results. Serious risk of bias was due to unclear allocation concealment and unclear to high risk of selective reporting. Indirectness was due to the differences between the outcomes of interest and those reported in the included studies.

Potential biases in the review process

A potential bias inherent in this review was the difference in outcome reporting and measurement for both our primary and secondary outcomes. For the outcome of reduction of overall or specific symptoms, we presented results as the proportion of children who had clinical improvement measured using symptoms and signs severity score, and not the absolute change of the scores. Similarly, we presented the results for changes in tympanometry measurement as the proportion of children who had resolution of middle ear effusion measured using pneumatic otoscope and tympanometry, rather than the absolute changes of middle ear pressure or the tympanogram curve types. This resolution was determined by the normalisation of tympanogram curve to type A curve (the absence of middle ear effusion).

Agreements and disagreements with other studies or reviews

A literature review of the effectiveness of corticosteroids in several acute respiratory infections (i.e. acute pharyngitis, community-acquired pneumonia, and AOM) similarly concluded that the effect of corticosteroids for AOM is still unknown due to insufficient evidence (Principi 2013). This review poorly reported the searching method or eligibility criteria, and the conclusion was based on only one RCT (Chonmaitree 2003).

AUTHORS' CONCLUSIONS

Implications for practice

Our review did not demonstrate that systemic corticosteroids improve important clinical outcomes in acute otitis media, and therefore has no implication for clinical practice.

Implications for research

Large, high-quality randomised controlled trials are needed to evaluate the effectiveness of corticosteroids in uncomplicated acute otitis media.

ACKNOWLEDGEMENTS

This review is part of a PhD project at the Centre for Research in Evidence-Based Practice, Bond University (CREBP) Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia. It is supported by the CREBP, Bond University.

We would especially like to thank Clare Dooley and Liz Dooley for their assistance in the preparation of the protocol. We wish to thank the following people for commenting on the draft protocol: Jean Symes, Zaina AlBalawi, Brian Westerberg, Simona Nistor-Grahl, Ravi Shankar, and Michelle Guppy. We thank the following people for commenting on the draft review: Shunjie Chua, Esther Martin Anna Granath, Mark Jones, and Michelle Guppy.

The methods section of this protocol is based on a standard template developed by Cochrane Airways and adapted by the Cochrane Acute Respiratory Infections Group.

REFERENCES

References to studies included in this review

Chonmaitree 2003 *{published data only}*
Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, et al. A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. *Journal of Pediatrics* 2003; **143**(3):377–85.

McCormick 2003 *{published data only}*
McCormick DP, Saeed K, Uchida T, Baldwin CD, Deskin R, Lett-Brown MA, et al. Middle ear fluid histamine and leukotrine B4 in acute otitis media: effect of antihistamine or corticosteroid treatment. *International Journal of Pediatric Otorhinolaryngology* 2003;**67**(3):221–30.

References to studies excluded from this review

Albernaz 2001 *{published data only}*
Albernaz PLM. What are the causes of obstructive tubing after acute otitis media (AOM) that has been treated with antibiotics? [Qual a conduta nos casos de obstrução tubária pós otite média aguda (OMA) devidamente tratada com antibióticos?]. *Acta WHO* 2001;**20**(3):129.

Arusgamov 1966 *{published data only}*
Arusgamov GA. Effectiveness of use of cortisone and hydrocortisone in treatment of suppurative diseases of the ear. *Voenno-Meditsinskii Zhurnal* 1966;**6**:42–5.

Cajgfinger 1967 *{published data only}*
Cajgfinger H, Gignoux M. On the local use of a new antibiotic-corticoid combination in acute otitis. *Lyon Medical* 1967;**217**(12):883–4.

Califano 2014 *{published data only}*
Califano L, Salafia F, Mazzone S, D'Ambrosio G, Malafronte L, Vassallo A. A comparative randomized study on the efficacy of a systemic steroid therapy vs. a thermal therapy in otitis media with effusion in children. *Minerva Pediatrica* 2016;**68**(4):241–9. [DOI: R15Y9999N00A140043

Capella 1984 *{published data only}*
Capella DG, Amador MT. Serous otitis media [Otitis media serosa]. *Anales Otorrinolaringologicos Iberoamericanos* 1984; **11**(3):195–220.

Carvalho 1984 *{published data only}*
Carvalho EDS. Corticosteroids in childhood infectious disease II - specific indications [Corticosteróides em infectologia infantil II – Indicações especificas]. *Journal de Pediatria* 1984;**56**(1-2):33–8.

Chinski 2003 *{published data only}*
Chinski A, Beider B, Luna MFR. Treatment of secretory otitis media: antibiotic + placebo versus antibiotic + steroids. 8th International Symposium on Recent Advances in Otitis Media; 3-7 June 2003; Fort Lauderdale, FL, USA. Hamilton, Ontario: BC Decker Inc, 2005:221.

Chirileanu 1978 *{published data only}*
Chirileanu C. Personal method of endotubal therapy [Metodă personalia de tuboterapie]. *Revista de Chirurgie, Oncologie, Radiologie, O. R. L., Oftalmologie, Stomatologie. Oftalmologie* 1978;**23**(3):181–4.

Choung 2008 *{published data only}*
Choung YH, Shin YR, Choi SJ, Park K, Park HY, Lee JB, et al. Management for the children with otitis media with effusion in the tertiary hospital. *Clinical and Experimental Otorhinolaryngology* 2009;**1**(4):201–5. [DOI: 10.3342/ceo.2008.1.4.201

Crysdale 1984 *{published data only}*
Crysdale WS. Medical management of serous otitis media. *Otolaryngologic Clinics of North America* 1984;**17**(4):653–7.

Daly 1991 *{published data only}*
Daly K, Giebink S, Batalden PB, Anderson RS, Le CT, Lindgren B. Resolution of otitis media with effusion with the use of a stepped treatment regimen of trimethoprim-sulfamethoxazole and prednisone. *Pediatric Infectious Disease Journal* 1991;**10**:500–6.

Endo 1997 *{published data only}*
Endo LH, Antunes AB, Vidolin C, Bilécki MM, Magalhães KVB. Secretory media otitis: clinical treatment vs. placebo [Otite média secretora: tratamento clinico versus placebo]. *Revista Brasileira de Otorrinolaringologia* 1997;**63**(2):116–9.

Fradis 1983 *{published data only}*
Fradis M. Steroid treatment for secretory otitis media. Ear, Nose & Throat Journal 1983; Vol. 62, issue 8:443–5.

Han 2009 *{published data only}*
Han Z, Zhibin C, Dengyuan W, Xia X, Xiaonian Z, Guangqian X. The therapeutic effects of oral administration and intratympanic injection of glucocorticoid in the

treatment of otitis media with effusion. *Journal of Audiology and Speech Pathology* 2009;**17**(6):560–2.

Hearey 1990 ***{published data only}***
Hearey C, Hokanson J, Ury H, Chang C, Coplan B, Hall M. Lack of efficacy of short-term prednisolone, trimethoprim-sulfamethoxazole, alone or combined, in persistent otitis media with effusion: season of entry as a possible determinant of outcome. *American Journal of Diseases of Childhood* 1990;**144**:420.

Hussein 2017 ***{published data only}***
Hussein A, Fathy H, Amin SM, Elsisy N. Oral steroids alone or followed by intranasal steroids versus watchful waiting in the management of otitis media with effusion. *Journal of Laryngology and Otology* 2017;**131**(10):907–13. [DOI: 10.1017/S0022215117001700

Martin 1975 ***{published data only}***
Martin H, Martin C. Clinical trial of polydexa in middle ear diseases [Essai clinique du polydexa dans les atteintes de l'oreille moyenne]. *Journal Francais d Oto-Rhino Laryngologie, Audiophonologie et Chirurgie Maxillo-Faciale* 1975;**24**(2):157–61.

Matsubara 2007 ***{published data only}***
Matsubara A. Diagnosis of and therapy for eosinophilic otitis media and paranasal sinusitis - preservation therapy for eosinophilic otitis media according to the classification. *Nippon Jibiinkoka Gakkai Kaiho [Journal of the Oto-Rhino-Laryngological Society of Japan]* 2007;**110**(3):91–4.

Oppenheimer 1968 ***{published data only}***
Oppenheimer P. Short-term steroid therapy - treatment of serous otitis media in children. *Archives of Otolaryngology* 1968;**88**(2):138–40.

Persico 1978 ***{published data only}***
Persico M, Podoshin L, Fradis M, Israel H. Otitis media with effusion: a steroid and antibiotic therapeutical trial before surgery. *Annals of Otology, Rhinology & Laryngology* 1978;**87**(2 Pt 1):191–6.

Puhakka 1985 ***{published data only}***
Puhakka H, Haapaniemi J, Tuohimaa P, Ruuskanen O, Eskola J. Peroral prednisolone in the treatment of middle-ear effusion in children: a double-blind study. *Auris Nasus Larynx* 1985;**12**(Suppl 1):268–71.

Pulkki 2006 ***{published data only}***
Pulkki J, Huikko S, Rautakorpi UL, Honkanen P, Klaukka T, Mäkela M, et al. Management of pain in acute otitis media in Finnish primary care. *Scandinavian Journal of Infectious Diseases* 2006;**38**(4):265–7.

Rosenfeld 1992 ***{published data only}***
Rosenfeld RM. New concepts for steroid use in otitis media with effusion. *Clinical Pediatrics* 1992;**31**(10):615–21.

Roydhouse 1978 ***{published data only}***
Roydhouse N. Middle ear problems in children: rational treatment. *Drugs* 1978;**15**(5):393–8.

Ruohola 1999 ***{published data only}***
Ruohola A, Heikkinen T, Jero J, Puhakka T, Juven T, Närkiö-Mäkelä M, et al. Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes. *Journal of Pediatrics* 1999; **134**(4):459–63.

Saffar 2001 ***{published data only}***
Saffar MJ, Nili H, Kosaryan M, sfahani M, Kasiri AM, Khalilian AR. Effect of prednisolone on otitis media with effusion. *Journal of Mazandaran University of Medical Sciences* 2001;**11**(33):14–9.

Schwartz 1979 ***{published data only}***
Schwartz RH, Puglese JP, Schwartz DM. Use of a short course of prednisone for treating middle ear effusion: a double-blind crossover study. *Journal of Allergy and Clinical Immunology* 1979;**63**(3 Pt 2):296–300.

Schwartz 1981 ***{published data only}***
Schwartz RH. Otitis media with effusion: results of treatment with a short course of oral prednisone or intranasal beclomethasone aerosol. *Otolaryngology. Head and Neck Surgery* 1981;**89**(3 Pt 1):386–91.

Seehusen 2012 ***{published data only}***
Seehusen DA, MacDonnell J. Steroids for the treatment of otitis media with effusion in children. *American Family Physician* 2012;**85**(3):235–6.

Sergienko 1975 ***{published data only}***
Sergienko PV, Pushkareva NS, El'chaninova II. Some aspects of the etiology, pathogenesis, clinical aspects and treatment of lingering forms of acute otitis media in children. *Zhurnal Ushnykh, Nosovykh i Gorlovykh Boleznei* 1975;**1**:40–5.

Terjung 1967 ***{published data only}***
Terjung VW. On the treatment of otitis media [Zur behandlung der otitis media]. *Hippokrates* 1967;**38**(17): 699–701.

Wang 2007 ***{published data only}***
Wang C, Liu Z, Huang X, Xu K. The curative effect of corticosteroid on acute otitis media with middle ear effusion. *Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi [Journal of Clinical Otorhinolaryngology, Head, & Neck Surgery]* 2007;**21**(4):167–8.

Woodhead 1986 ***{published data only}***
Woodhead JC, Milavetz G, Dusdieker LB, Booth BM, Wilmoth RN. Prednisone treatment of otitis media with effusion. *American Journal of Diseases of Children* 1986;**140**: 318.

Additional references

Atkins 2004
Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**(7454):1490.

Bertin 1996
Bertin L, Pons G, d'Athis P, Duhamel JF, Maudelonde C, Lasfargues G, et al. A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis

media. *Fundamental & Clinical Pharmacology* 1996;**10**(4): 387–92.

Boluyt 2008
Boluyt N, Tjosvold L, Lefebvre C, Klassen TP, Offringa M. Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. *Archives of Pediatrics and Adolescent Medicine* 2008;**162**(2):111–6. [DOI: 10.1001/archpediatrics.2007.40

Bradley-Stevenson 2007
Bradley-Stevenson C, O'Neill P, Roberts T. Otitis media in children (acute). Clinical Evidence 2007; Vol. 8:301.

Brouwer 2015
Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD004405.pub5

Chonmaitree 2008
Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, et al. Viral upper respiratory tract infection and otitis media complication in young children. *Clinical Infectious Diseases* 2008;**46**(6):815–23. [DOI: 10.1086/528685

Coleman 2008
Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD001727.pub4

Coutinho 2011
Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Molecular and Cellular Endocrinology* 2011;**335**(1):2–13.

Deshmukh 2007
Deshmukh CT. Minimizing side effects of systemic corticosteroids in children. *Indian Journal of Dermatology, Venereology and Leprology* 2007;**73**(4):218–21.

Foxlee 2011
Foxlee R, Johansson AC, Wejfalk J, Dooley L, Del Mar CB. Topical analgesia for acute otitis media. *Cochrane Database of Systematic Reviews* 2011, Issue 8. [DOI: 10.1002/14651858.CD005657.pub2

GRADE 2004
GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version (accessed prior to 1 March 2018). Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Gribben 2012
Gribben B, Salkeld LJ, Hoare S, Jones HF. The incidence of acute otitis media in New Zealand children under five years of age in the primary care setting. *Journal of Primary Health Care* 2012;**4**(3):205–12.

Gunasekera 2007
Gunasekera H, Knox S, Morris P, Britt H, McIntyre P, Craig JC. The spectrum and management of otitis media in Australian Indigenous and non-Indigenous children: a national study. *Pediatric Infectious Disease Journal* 2007;**26**(8):689–92.

Gupta 2008
Gupta P, Bhatia V. Corticosteroid physiology and principles of therapy. *Indian Journal of Pediatrics* 2008;**75**(10): 1039–44.

Hayward 2012
Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ. Corticosteroids as standalone or add-on treatment for sore throat. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: 10.1002/14651858.CD008268.pub2

Higgins 2011
Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Juhn 2008
Juhn SK, Jung MK, Hoffman MD, Drew BR, Preciado DA, Sausen NJ, et al. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. *Clinical and Experimental Otorhinolaryngology* 2008;**1**(3):117–38.

Kitamura 2015
Kitamura K, Iino Y, Kamide Y, Kudo F, Nakayama T, Suzuki K, et al. Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan - 2013 update. *Auris Nasus Larynx* 2015;**42**(2): 99–106.

Lee 2012
Lee HJ, Park SK, Choi KY, Park SE, Chun YM, Kim KS, et al. Korean clinical practice guidelines: otitis media in children. *Journal of Korean Medical Science* 2012;**27**(8): 835–48.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lieberthal 2013
Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. *Pediatrics* 2013;**131**(3): e964–99.

Moher 2010
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *International Journal of Surgery* 2010;**8**(5):336–41.

Morris 2009
Morris PS, Leach AM. Managing otitis media: an evidence-based approach. *Australian Prescriber* 2009;**32**(6):155–9.

NSW Health 2014
NSW Health. Infants and children, otitis media: acute management of sore ear, second edition. www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2014_023.pdf (accessed prior to 11 March 2018).

Pichichero 2000
Pichichero ME. Recurrent and persistent otitis media. *Pediatric Infectious Disease Journal* 2000;**19**(9):911–6.

Pichichero 2015
Pichichero ME, Casey JR. Acute otitis media: update 2015. contemporarypediatrics.modernmedicine.com/contemporary-pediatrics/news/acute-otitis-media-update-2015 (accessed prior to 11 March 2018).

Principi 2013
Principi N, Bianchini S, Baggi E, Esposito S. No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media. *European Journal of Clinical Microbiology and Infectious Diseases* 2012;**32**(2):151–60.

Principi 2017
Principi N, Marchisio P, Rosazza C, Sciarrabba CS, Esposito S. Acute otitis media with spontaneous tympanic membrane perforation. *European Society of Clinical Microbiology* 2017; **36**:11–8.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

SACHCN 2014
South Australian Child Health Clinical Network. South Australian Paediatric Practice Guidelines - Acute otitis media in children. www.sahealth.sa.gov.au/wps/wcm/connect/a8910c004329b4dc81b8ed8bf287c74e/Acute%2BOtitis%2BMedia%2Bin%2Bchildren_May2014.pdf?MOD=AJPERES&CACHE=NONE&CONTENT-CACHE=NONE (accessed prior to 11 March 2018).

Simpson 2011
Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. *Cochrane Database of Systematic Reviews* 2011, Issue 5. [DOI: 10.1002/14651858.CD001935.pub3

Slovik 2008
Slovik Y, Raiz S, Leiberman A, Puterman M, Dagan R, Leibovitz E. Rates of tympanic membrane closure in double-tympanocentesis studies. *Pediatric Infectious Disease Journal* 2008;**27**(6):490–3.

Tikaram 2012
Tikaram A, Chew YK, Zulkiflee AB, Chong AW, Prepageran N. Prevalence and risk factors associated with otitis media with effusion in children visiting tertiary care centre in Malaysia. *International Medical Journal Malaysia* 2012;**11** (1):37–40.

Timmerman 2007
Timmerman AA, Meesters CMG, Speyer R, Anteunis LJC. Psychometric qualities of questionnaires for the assessment of otitis media impact. *Clinical Otolaryngology* 2007;**32**(6): 429–39.

Ting 2012
Ting PJ, Lin CH, Huang FL, Lin MC, Hwang KP, Huang YC, et al. Epidemiology of acute otitis media among young children: a multiple database study in Taiwan. *Journal of Microbiology, Immunology and Infection* 2012;**45**(6):453–8.

Umar 2013
Umar S, Restuti RD, Suwento R, Priyono H, Mansyur M. The prevalence and risk factors of acute otitis media in children in the municipality of East Jakarta [Prevalensi dan faktor risiko otitis media akut pada anak–anak di kotamadya Jakarta Timur]. lib.ui.ac.id/naskahringkas/2015-09/SP-Sakina%20Umar (accessed prior to 11 March 2018).

UNICEF 2011
United Nations Children's Fund (UNICEF). The emerging generation. The State of the World's Children 2011. Adolescence: an Age of Opportunity 2011:1–15. [ISBN: 978–92–806–4555–2]

Venekamp 2014
Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar CB, Perera R, et al. Systemic corticosteroids for acute sinusitis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD008115.pub3

Venekamp 2015
Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD000219.pub4

Vergison 2010
Vergison A, Dagan R, Arguedas A, Bonhoeffer J, Cohen R, DHooge I, et al. Otitis media and its consequences: beyond the earache. *Lancet Infectious Diseases* 2010;**10**:195–203.

References to other published versions of this review

Ranakusuma 2016
Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, et al. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2016, Issue 7. [DOI: 10.1002/14651858.CD012289

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chonmaitree 2003

Methods	**Randomised:** yes, it was computer-generated with block randomisation (RCT) **Concealment of allocation:** yes, the list of randomisation was in codes and only the statistician who had generated the randomisation was aware of the code **Double-blind:** yes, syrups similar in taste and colour to prednisolone were used as placebo **Intention-to-treat:** not an ITT analysis. Analysis was done on children who had more than 70% adherence. Adherence to treatment was assessed by diary and the weight of medication bottles (available-case analysis) **Loss to follow-up:** unclear **Design:** 2 x 2 factorial design
Participants	**N:** 198 children (N = 179 children included in analysis) **Age:** 3 months to 6 years **Setting:** the paediatric outpatient clinic of the University of Texas Medical Branch at Galveston, USA **Inclusion criteria:** (1) children who had experienced 2 or more previous AOM episodes (with the first AOM episode before 1 year of age) or (2) infants younger than 6 months of age having the first or second episode of AOM **Exclusion criteria:** children who had: (1) anatomic or physiologic defect of the ear or nasopharynx; (2) major medical condition; (3) other concurrent medication; (4) received antibiotic treatment within 1 week; (5) history of previous allergic reaction to cephalosporin drugs; (6) indwelling tympanostomy tube; (7) history of exposure to an individual with chickenpox in the previous 3 weeks **Baseline characteristics:** most of the baseline characteristics were balanced except for breastfeeding and fever. There were fewer numbers of children in the corticosteroid group compared to the placebo group in terms of breastfeeding (16% versus 34%) and clinical symptoms of fever (49% versus 63%)
Interventions	All children received single-dose antibiotic intramuscular injections of ceftriaxone (50 mg/kg) and were randomised to either: **Intervention:** corticosteroid (prednisolone) 2 mg/kg per day in 3 divided doses for 5 days (N = 89), or **Comparison:** matching placebo for 5 days (N = 90) Due to the factorial design, the corticosteroid group was a combination of a corticosteroid-only group (prednisolone 2 mg/kg per day in 3 divided doses; N = 45) and corticosteroid plus antihistamine group (prednisolone plus chlorpheniramine maleate; N = 44). The placebo group was a combination of an antihistamine group (chlorpheniramine maleate; N = 44) and a double placebo group (N = 46). We therefore analysed the outcomes of prednisolone versus placebo
Outcomes	**Primary outcomes** 1. Treatment failure defined as persistent clinical symptoms (i.e. fever > 38 °C rectally, ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, watery eyes) with inflamed tympanic membrane at either visit 2 (Day 5) or

	visit 3 (Day 14) that required additional antibiotic treatment 2. Duration of middle ear effusion 3. AOM recurrence during the first 6 months **Secondary outcomes** 1. Reduction of symptom severity scores: fever > 38 °C rectally, ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, watery eyes with the range of zero (none) to 2 (severe) and sign severity scores. The sign severity scores were characterised by: position (0 = normal to 2 = bulging), colour/transparency (0 = shiny to 2 = red/yellow), and mobility (0 = normal to 2 = non-mobile) with 6 as the maximum otoscopic score. 2. Presence of middle ear effusion measured using tympanometry 3. Side effects
Notes	1. Information on the randomisation and concealment of allocation was not provided in the published paper, therefore we contacted the trial author to retrieve this information 2. Data of sign and symptom severity scores and side effects from each group at various time points were not provided in the published paper. The trial author was not able to provide this information 3. Out of 198 randomised children, 19 were not analysed (9.6%). However, the allocation of these children to their treatment group was evenly distributed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated based on additional information obtained from the trial author
Allocation concealment (selection bias)	Unclear risk	There was no clear description of how the allocation was concealed. We contacted the trial author, who merely reported that only the statistician who generated the randomisation schedule knew the code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "colored syrups similar to the drugs in taste and color were used as the placebos"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Based on additional information obtained from the trial author, the clinicians as the outcome assessors were not aware of the codes or the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 children (9.6%) were excluded from the analysis due to their non-adherence to the treatment drug and the follow-up visits and have not been analysed. However, their dis-

Chonmaitree 2003 (*Continued*)

		tribution into each treatment group was generally even
Selective reporting (reporting bias)	Unclear risk	We could not retrieve the trial protocol. Despite this study being registered in the clinical trial registry, the primary or secondary outcomes were not clearly described
Other bias	Low risk	No other bias detected. We contacted the trial author, who declared that there was no scientific or financial contribution from the pharmaceutical industry

McCormick 2003

Methods	**Randomised:** yes, it was computer-generated with block randomisation (RCT) **Concealment of allocation:** yes, the list of randomisation was in codes and only the statistician who had generated the randomisation was aware of the code **Double-blind:** syrups similar to prednisolone in taste and colour were used as placebo **Intention-to-treat:** not an ITT analysis. Analysis was done on children who had more than 70% adherence. Adherence to treatment was assessed by diary and medication bottle weight (available-case analysis) **Loss to follow-up:** unclear **Design:** 2 x 2 factorial design
Participants	**N:** 80 children (N = 73 children included in analysis) **Age:** 3 months to 6 years **Setting:** the paediatric outpatient clinic of the University of Texas Medical Branch at Galveston, USA **Inclusion criteria:** acute otitis media was diagnosed based on: (1) acute symptoms (i.e. fever, irritability, ear pain, lack of appetite, or lack of sleep); (2) signs of acute inflammation of the tympanic membrane (i.e. red, yellow, or bulged tympanic membrane); and (3) the presence of middle ear effusion identified with tympanocentesis procedure **Exclusion criteria:** children who had: (1) received treatment for AOM in the preceding 30 days; (2) received antibiotic treatment within 1 week; (3) allergy to treatment medication; (4) other concurrent medication; (5) perforation of the tympanic membrane or with tympanostomy tube(s); (6) a major medical condition or immunologic disorders; (7) anatomic or physiologic defect of the ear or nasopharynx; (8) been exposed to chickenpox during the past 3 weeks **Baseline characteristics:** most of the baseline characteristics were balanced except day-care attendance and passive smoking. There were fewer numbers of children in the corticosteroid group compared to placebo group who had attended a day-care centre (30% versus 45%), and there were more children in the corticosteroid group compared to the placebo group who had been exposed to smoking (50% versus 35%)
Interventions	All children received single-dose antibiotic intramuscular injection of ceftriaxone (50 mg/kg) and were randomised to either: **Intervention:** corticosteroid (prednisolone) 2 mg/kg per day in 3 divided doses for 5

	days (N = 37), or **Comparison:** matching placebo for 5 days (N = 36). Due to the factorial design, the corticosteroid group was a combination of a corticosteroid-alone group (prednisolone 2 mg/kg per day in 3 divided doses; N = 18) and corticosteroid plus antihistamine group (prednisolone plus chlorpheniramine maleate; N = 19). The placebo group was a combination of an antihistamine group (chlorpheniramine maleate; N = 18) and a double placebo group (N = 18). We therefore analysed the outcomes of prednisolone versus placebo
Outcomes	**Primary outcomes** 1. Total outcome defined as clinical outcomes at visit 2 (Day 4 to Day 6) and visit 3 (Day 14) and bacterial outcome at visit 2 2. The changes in histamine and leukotriene B4 (LTB4) in the middle ear fluid taken by tympanocentesis at the baseline and visit 2 (Day 4 to Day 6) **Secondary outcomes** 1. The duration of the middle ear effusion 2. AOM recurrence during the first 4 months following the baseline visit
Notes	1. Information on the randomisation and concealment of allocation was not provided in the published paper, therefore we contacted the trial author to retrieve this information 2. Data on clinical outcomes at visit 2 and visit 3 were not provided in the published paper. The trial author was not able to provide this information 3. Out of 80 randomised children, 7 children were not analysed (8.7%). However, the allocation of these children to their treatment group was evenly distributed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated based on additional information obtained from the trial author
Allocation concealment (selection bias)	Unclear risk	There was no clear description of how the allocation was concealed. We contacted the trial author, who merely reported that only the statistician who generated the randomisation schedule knew the code and that neither the parent nor the examining physician was informed of the type of treatment given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A light straw-colored solution similar to the drug was used as the placebo"

McCormick 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the parent nor the examining physician was informed of the type of treatment given"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Seven cases were lost to follow-up after the enrolment visit" 7 children (8.7%) who were lost to follow-up after randomisation were excluded from the analysis. However, their distribution into each treatment group was generally even
Selective reporting (reporting bias)	High risk	The authors did not report the clinical outcome at visit 2 (Day 4 to Day 6) and visit 3 (Day 14). This information was crucial to determine the total outcome. We also could not retrieve the trial protocol, and neither the primary nor secondary outcomes were clearly described in the clinical trial registry
Other bias	Low risk	We detected no other bias. We contacted the trial author, who declared that there was no scientific or financial contribution from the pharmaceutical industry

AOM: acute otitis media
ITT: intention-to-treat
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albernaz 2001	**STUDY DESIGN** Study was a literature review (non-English language article)
Arusgamov 1966	**PARTICIPANTS** Adults only (non-English language article)
Cajgfinger 1967	**INTERVENTIONS** Trial using topical or ear drop corticosteroid instead of systemic corticosteroid (non-English language article)
Califano 2014	**PARTICIPANTS** Trial including non-acute otitis media effusion

(*Continued*)

Capella 1984	**STUDY DESIGN** Study was a retrospective observation using medical records (non-English language article)
Carvalho 1984	**STUDY DESIGN** Study was a literature review (non-English language article)
Chinski 2003	**PARTICIPANTS** Trial including non-acute otitis media effusion (more than 2 months)
Chirileanu 1978	**INTERVENTIONS** Trial using an invasive intervention method by opening Eustachian tube ostium employing a probe and not using a systemic corticosteroid (non-English language article)
Choung 2008	**PARTICIPANTS** Trial excluding children with acute otitis media
Crysdale 1984	**STUDY DESIGN** Study was a literature review.
Daly 1991	**OTHERS** Children eligible to receive corticosteroid treatment were those whose otitis media effusion did not improve after 2 weeks of antibiotic treatment
Endo 1997	**PARTICIPANTS** Trial including children with persistent middle ear effusion for more than 3 months (non-English article)
Fradis 1983	**STUDY DESIGN** Study was a letter to the Editor
Han 2009	**COMPARATORS** Study was a quasi-randomised controlled trial and did not use placebo as a comparator (non-English language article)
Hearey 1990	**PARTICIPANTS** Trial including children with longstanding effusion for more than 10 weeks
Hussein 2017	**PARTICIPANTS** Trial including children with chronic middle ear effusion
Martin 1975	**INTERVENTIONS** Trial using topical or ear drop corticosteroid instead of systemic corticosteroid (non-English article)
Matsubara 2007	**STUDY DESIGN** Study was a literature review (non-English article)
Oppenheimer 1968	**ALLOCATION** Trial was a non-randomised study and did not include a placebo

(*Continued*)

Persico 1978	**ALLOCATION** Trial was a non-randomised study and did not include a placebo
Puhakka 1985	**PARTICIPANTS** Trial excluding children who had an acute otitis media episode during the preceding 3 months
Pulkki 2006	**STUDY DESIGN** Study was a retrospective observation using medical records
Rosenfeld 1992	**STUDY DESIGN** Study was a literature review
Roydhouse 1978	**STUDY DESIGN** Study was a literature review
Ruohola 1999	**PARTICIPANTS** Trial including children with tympanostomy tubes
Saffar 2001	**PARTICIPANTS** Trial including children with otitis media with effusion for more than 3 months
Schwartz 1979	**PARTICIPANTS** Trial including children with persistent otitis media effusion for 3 weeks or more
Schwartz 1981	**PARTICIPANTS** Trial including children with persistent otitis media effusion for 3 weeks or more
Seehusen 2012	**STUDY DESIGN** Study was a clinical scenario
Sergienko 1975	**ALLOCATION** Study was a non-randomised controlled trial (pre- and post study)
Terjung 1967	**INTERVENTIONS** Trial using topical or ear drop corticosteroid instead of systemic corticosteroid (non-English article)
Wang 2007	**COMPARATORS** Study did not use placebo as a comparator (non-English article)
Woodhead 1986	**PARTICIPANTS** Trial including children without inflammation signs of the tympanic membrane

Several articles did not provide abstracts or provided an unclear definition of otitis media effusion in their abstracts. We therefore had to retrieve the full text, and they were not included in our eligibility criteria (e.g. literature reviews, non-acute otitis media studies).

DATA AND ANALYSES

Comparison 1. Systemic corticosteroids versus placebo for children with acute otitis media

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of overall or specific symptoms at various time points	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 5	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Changes in tympanometry measurement at various time points	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Month 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Month 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Month 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 AOM recurrence at various time points	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Month 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Month 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Month 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 During Month 4 to Month 6	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

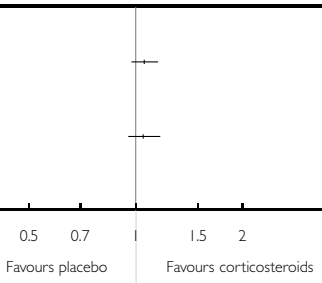
Analysis 1.1. Comparison 1 Systemic corticosteroids versus placebo for children with acute otitis media, Outcome 1 Reduction of overall or specific symptoms at various time points.

Review: Systemic corticosteroids for acute otitis media in children

Comparison: 1 Systemic corticosteroids versus placebo for children with acute otitis media

Outcome: 1 Reduction of overall or specific symptoms at various time points

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Day 5				
Chonmaitree 2003	84/89	80/90		1.06 [0.97, 1.16]
2 Day 14				
Chonmaitree 2003	81/89	78/90		1.05 [0.95, 1.17]

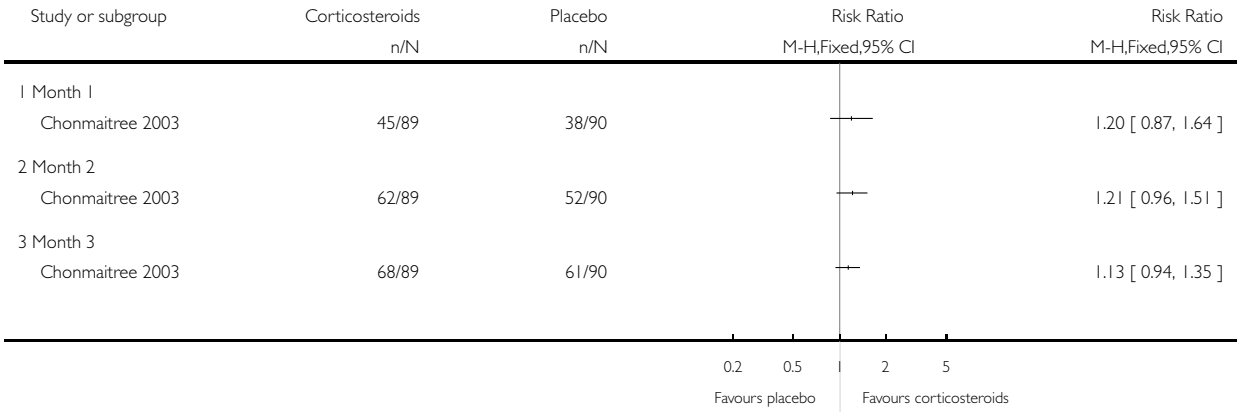


Analysis 1.2. Comparison 1 Systemic corticosteroids versus placebo for children with acute otitis media, Outcome 2 Changes in tympanometry measurement at various time points.

Review: Systemic corticosteroids for acute otitis media in children

Comparison: 1 Systemic corticosteroids versus placebo for children with acute otitis media

Outcome: 2 Changes in tympanometry measurement at various time points

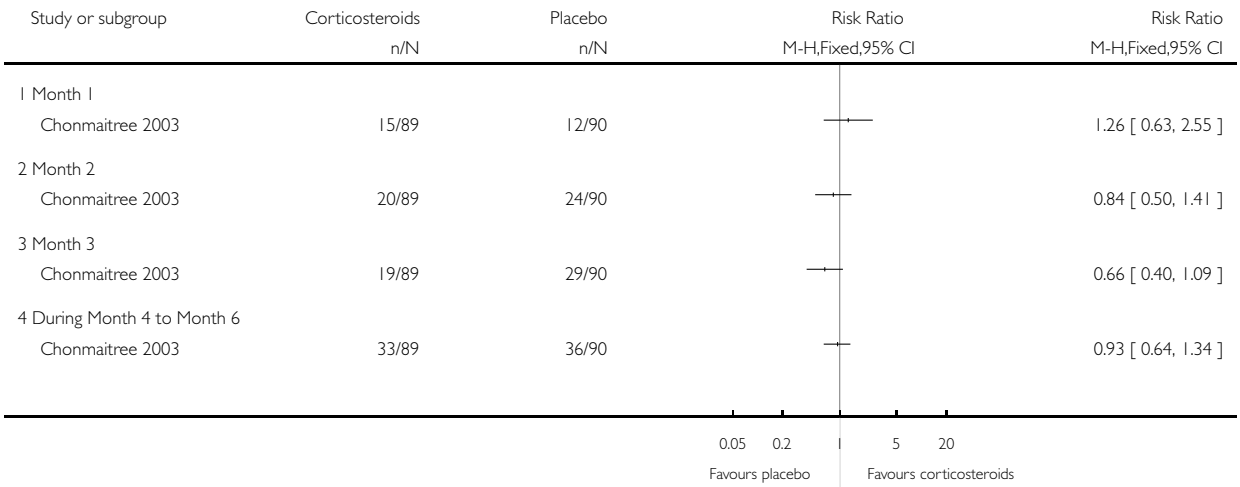


Analysis 1.3. Comparison 1 Systemic corticosteroids versus placebo for children with acute otitis media, Outcome 3 AOM recurrence at various time points.

Review: Systemic corticosteroids for acute otitis media in children

Comparison: 1 Systemic corticosteroids versus placebo for children with acute otitis media

Outcome: 3 AOM recurrence at various time points



APPENDICES

Appendix 1. CENTRAL (Cochrane Library)

#1MeSH descriptor: [Otitis Media] explode all trees
#2otitis media:ti,ab,kw (Word variations have been searched)
#3"middle ear" near/5 (infect* or inflam* or effusion):ti,ab,kw (Word variations have been searched)
#4ome or aom:ti,ab,kw (Word variations have been searched)
#5#1 or #2 or #3 or #4
#6MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#7adrenal cortex hormone*:ti,ab,kw (Word variations have been searched)
#8corticosteroid* or corticoid* or steroid* or glucocorticoid*:ti,ab,kw (Word variations have been searched)
#9MeSH descriptor: [Pregnenediones] explode all trees
#10pregnenedione* or pregnenolone* or hydrocortisone* or hydroxypregnenolone* or tetrahydrocortisol* or cortodoxone* or cortone acetate or cortisone or corticosterone:ti,ab,kw (Word variations have been searched)
#11aristocort or triamcinolone:ti,ab,kw (Word variations have been searched)
#12deltasone or prednisone or prednicot:ti,ab,kw (Word variations have been searched)
#13prednisolone or bubbli-pred or cotolone or prelone or pediapred or pms-prednisolone:ti,ab,kw (Word variations have been searched)
#14paramethasone or methylprednisolone or baycadron or dexamethasone or decadron:ti,ab,kw (Word variations have been searched)
#15clobetasol or beclomethasone or betamethasone or budesonide:ti,ab,kw (Word variations have been searched)

#16efcortesol or hydrocortone or solu-cortef or cortef or A-Hydrocort:ti,ab,kw (Word variations have been searched)
#17betnelan or betnesol or celestone:ti,ab,kw (Word variations have been searched)
#18deflazacort or calcort:ti,ab,kw (Word variations have been searched)
#19medrone or medrol or solu-medrone or depo-medrone or methylpred-DP:ti,ab,kw (Word variations have been searched)
#20kenalog or novolizer or pulmicort or symbicort or entocort EC:ti,ab,kw (Word variations have been searched)
#21beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte:ti,ab,kw (Word variations have been searched)
#22cortisol:ti,ab,kw (Word variations have been searched)
#23MeSH descriptor: [Mineralocorticoids] explode all trees
#24mineralocorticoid* or mineralcorticoid*:ti,ab,kw (Word variations have been searched)
#25MeSH descriptor: [Aldosterone] explode all trees
#26aldosterone or florinef acetate or fludrocortisone:ti,ab,kw (Word variations have been searched)
#27#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28#5 and #27 in Trials

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Otitis Media/
2 otitis media.tw.
3 (middle ear adj5 (infect* or inflam* or effus*)).tw.
4 (ome or aom).tw.
5 or/1-4
6 exp Adrenal Cortex Hormones/
7 adrenal cortex hormone*.tw,nm.
8 corticosteroid*.tw,nm.
9 corticoid*.tw,nm.
10 steroid*.tw,nm.
11 glucocorticoid*.tw,nm.
12 exp Pregnenediones/
13 pregnenedione*.tw,nm.
14 pregnenolone*.tw,nm.
15 hydrocortisone.tw,nm.
16 hydroxypregnenolone.tw,nm.
17 tetrahydrocortisol.tw,nm.
18 cortodoxone.tw,nm.
19 (cortone acetate or cortisone).tw,nm.
20 corticosterone.tw,nm.
21 (aristocort or triamcinolone).tw,nm.
22 (deltasone or prednisone or prednicot).tw,nm.
23 (prednisolone or bubbli-pred or cotolone or prelone or pediapred or pms-prednisolone).tw,nm.
24 paramethasone.tw,nm.
25 methylprednisolone.tw,nm.
26 (baycadron or dexamethasone or decadron).tw,nm.
27 clobetasol.tw,nm.
28 beclomethasone.tw,nm.
29 betamethasone.tw,nm.
30 budesonide.tw,nm.
31 (efcortesol or hydrocortone or solu-cortef or cortef or A-Hydrocort).tw,nm.
32 (betnelan or betnesol or celestone).tw,nm.
33 (deflazacort or calcort).tw,nm.
34 (medrone or medrol or solu-medrone or depo-medrone or methylpred-DP).tw,nm.

35 kenalog.tw,nm.
36 (novolizer or pulmicort or symbicort or entocort EC).tw,nm.
37 (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm.
38 cortisol.tw,nm.
39 exp Mineralocorticoids/
40 mineralocorticoid*.tw. or mineralcorticoid*.tw,nm.
41 Aldosterone/
42 aldosterone.tw,nm.
43 (florinef acetate or fludrocortisone).tw,nm.
44 or/6-43
45 5 and 44

Appendix 3. Embase (Elsevier) search strategy

#31	**#27** AND **#30**	
#30	**#28** OR **#29**	
#29	**random***:ab,ti OR **placebo***:ab,ti OR **crossover***:ab,ti OR **'cross-over'**:ab,ti OR **factorial**:ab,ti OR **volunteer***:ab,ti OR **allocat***:ab,ti OR **assign***:ab,ti OR ((**singl*** OR **doubl***) NEAR/2 **blind***):ab,ti AND [embase]/lim	
#28	**'single blind procedure'**/de OR **'double blind procedure'**/de OR **'crossover procedure'**/exp OR **'randomized controlled trial'**/de	
#27	**#5** AND **#26**	
#26	**#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25**	
#25	**aldosterone**:ab,ti OR **'florinef acetate'**:ab,ti OR **fludrocortisone**:ab,ti AND [embase]/lim	
#24	**'aldosterone'**/de AND [embase]/lim	
#23	**mineralcorticoid***:ab,ti OR **mineralocorticoid***:ab,ti AND [embase]/lim	
#22	**'mineralocorticoid'**/exp AND [embase]/lim	
#21	**cortisol**:ab,ti AND [embase]/lim	
#20	**beclometasone**:ab,ti OR **aerobec**:ab,ti OR **asmabec**:ab,ti OR **beclazone**:ab,ti OR **becodisks**:ab,ti OR **becotide**:ab,ti OR **'clenil modulite'**:ab,ti OR **qvar**:ab,ti OR **becloforte**:ab,ti AND [embase]/lim	

(*Continued*)

#19	**novolizer**:ab,ti OR **pulmicort**:ab,ti OR **symbicort**:ab,ti OR **'entocort ec'**:ab,ti AND [embase]/lim	
#18	**kenalog**:ab,ti AND [embase]/lim	
#17	**medrone**:ab,ti OR **medrol**:ab,ti OR **'solu-medrone'**:ab,ti OR **'depo-medrone'**:ab,ti OR **'methylpred-dp'**:ab,ti AND [embase]/lim	
#16	**deflazacort**:ab,ti OR **calcort**:ab,ti AND [embase]/lim	
#15	**betnelan**:ab,ti OR **betnesol**:ab,ti OR **celestone**:ab,ti AND [embase]/lim	
#14	**clobetasol**:ab,ti OR **beclomethasone**:ab,ti OR **betamethasone**:ab,ti OR **budesonide**:ab,ti OR **efcortesol**:ab,ti OR **hydrocortone**:ab,ti OR **'solu-cortef'**:ab,ti OR **cortef**:ab,ti OR **'a-hydrocort'**:ab,ti AND [embase]/lim	
#13	**paramethasone**:ab,ti OR **methylprednisolone**:ab,ti OR **baycadron**:ab,ti OR **dexamethasone**:ab,ti OR **decadron**:ab,ti AND [embase]/lim	
#12	**prednisolone**:ab,ti OR **'bubbli-pred'**:ab,ti OR **cotolone**:ab,ti OR **prelone**:ab,ti OR **pediapred**:ab,ti OR **'pms-prednisolone'**:ab,ti AND [embase]/lim	
#11	**pregnenedione***:ab,ti OR **pregnenolone***:ab,ti OR **hydrocortisone**:ab,ti OR **hydroxypregnenolone**:ab,ti OR **tetrahydrocortisol**:ab,ti OR **cortodoxone**:ab,ti OR **'cortone acetate'**:ab,ti OR **cortisone**:ab,ti OR **corticosterone**:ab,ti OR **aristocort**:ab,ti OR **triamcinolone**:ab,ti OR **deltasone**:ab,ti OR **prednisone**:ab,ti OR **prednicot**:ab,ti AND [embase]/lim	
#10	**'pregnane derivative'**/de AND [embase]/lim	
#9	**corticoid***:ab,ti OR **steroid***:ab,ti OR **glucocorticoid***:ab,ti AND [embase]/lim	
#8	**corticosteroid***:ab,ti AND [embase]/lim	
#7	**'adrenal cortex hormone'**:ab,ti OR **'adrenal cortex hormones'**:ab,ti AND [embase]/lim	
#6	**'corticosteroid'**/exp AND [embase]/lim	
#5	**#1** OR **#2** OR **#3** OR **#4**	

(*Continued*)

#4	**ome**:ab,ti OR **aom**:ab,ti AND [embase]/lim	
#3	(**'middle ear'** NEAR/5 (**infect*** OR **inflam*** OR **effusion**)): ab,ti AND [embase]/lim	
#2	**'otitis media'**:ab,ti AND [embase]/lim	
#1	**'otitis media'**/exp AND [embase]/lim	

Appendix 4. CINAHL (EBSCO) search strategy

S1	(MH "Otitis Media+")
S2	TI otitis media OR AB otitis media
S3	TI (middle ear N5 (infect* or inflam* or effusion)) OR AB (middle ear N5 (infect* or inflam* or effusion))
S4	TI (ome or aom) OR AB (ome or aom)
S5	S1 OR S2 OR S3 OR S4
S6	(MH "Adrenal Cortex Hormones+")
S7	TI adrenal cortex hormone* OR AB adrenal cortex hormone
S8	TI (corticosteroid* or corticoid* or steroid* or glucocorticoid*) OR AB (corticosteroid* or corticoid* or steroid* or glucocorticoid*)
S9	TI (pregnenedione* or pregnenolone* or hydrocortisone* or hydroxypregnenolone* or tetrahydrocortisol* or cortodoxone*) OR AB (pregnenedione* or pregnenolone* or hydrocortisone* or hydroxypregnenolone* or tetrahydrocortisol* or cortodoxone*)
S10	TI (aristocort or triamcinolone) OR AB (aristocort or triamcinolone)
S11	TI (prednisolone or bubbli-pred or cotolone or prelone or pediapred or pms-prednisolone) OR AB (prednisolone or bubbli-pred or cotolone or prelone or pediapred or pms-prednisolone)
S12	TI (paramethasone or methylprednisolone) OR AB (paramethasone or methylprednisolone)
S13	TI (baycadron or dexamethasone or decadron) OR AB (baycadron or dexamethasone or decadron)
S14	TI (clobetasol or beclomethasone or betamethasone or budesonide) OR AB (clobetasol or beclomethasone or betamethasone or budesonide)

(*Continued*)

S15	TI (efcortesol or hydrocortone or solu-cortef or cortef or A-Hydrocort) OR AB (efcortesol or hydrocortone or solu-cortef or cortef or A-Hydrocort)
S16	TI (betnelan or betnesol or celestone) OR AB (betnelan or betnesol or celestone)
S17	TI (deflazacort or calcort) OR AB (deflazacort or calcort)
S18	TI (medrone or medrol or solu-medrone or depo-medrone or methylpred-DP) OR AB (medrone or medrol or solu-medrone or depo-medrone or methylpred-DP)
S19	TI kenalog OR AB kenalog
S20	TI (novolizer or pulmicort or symbicort or entocort EC) OR AB (novolizer or pulmicort or symbicort or entocort EC)
S21	TI (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte) OR AB (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte)
S22	TI cortisol OR AB cortisol
S23	(MH "Mineralocorticoids+")
S24	TI (mineralcorticoid* or mineralocorticoid*) OR AB (mineralcorticoid* or mineralocorticoid*)
S25	(MH "Aldosterone")
S26	TI aldosterone OR AB aldosterone
S27	TI (florinef acetate or fludrocortisone) OR AB (florinef acetate or fludrocortisone)
S28	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
S29	S5 AND S28
S30	(MH "Clinical Trials+")
S31	PT clinical trial
S32	TI clinic* N1 trial* OR AB clinic* N1 trial*
S33	TI ((singl* or doubl* or tripl* or trebl*) N1 (mask* or blind*)) OR AB ((singl* or doubl* or tripl* or trebl*) N1 (mask* or blind*))
S34	(MH "Random Assignment")
S35	TI random* OR AB random*
S36	(MH "Placebos")

(*Continued*)

S37	TI placebo* OR AB placebo*
S38	S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S39	S29 AND S38

Appendix 5. Web of Science (Thomson Reuters) search strategy

#4 AND #3 **Refined by: PUBLICATION YEARS:** (2016 OR 2017) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years
#4 AND #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years
TOPIC: (random* or placebo* or crossover* or "cross over" or allocat* or ((singl* or doubl*) NEAR/1 blind*)) *OR* **TITLE:** (trial) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years
#2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years
TOPIC: ("adrenal cortex hormone*" or corticosteroid* or corticoid* or steroid* or glucocorticoid*) *OR* **TOPIC:** (pregnenedione* or pregnenolone* or hydrocortisone or hydroxypregnenolone or tetrahydrocortisol or cortodoxone or "cortone acetate" or cortisone or corticosterone or aristocort or triamcinolone or deltasone or prednisone or prednicot or prednisolone) *OR* **TOPIC:** ("bubbli-pred" or cotolone or prelone or pediapred or "pms-prednisolone" or paramethasone or methylprednisolone or baycadron or dexamethasone or decadron or clobetasol or beclomethasone or betamethasone or budesonide or efcortesol or hydrocortone or solu-cortef or cortef or A-Hydrocort or betnelan) *OR* **TOPIC:** (betnesol or celestone or deflazacort or calcort or medrone or medrol or solu-medrone or depo-medrone or methylpred-DP or kenalog or novolizer or pulmicort or symbicort or entocort or beclometasone or aerobec or asmabec or beclazone or becodisks or becotide) *OR* **TOPIC:** ("clenil modulite" or qvar or becloforte or cortisol or mineralcorticoid* or aldosterone or "florinef acetate" or fludrocortisone) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years
TOPIC: ("otitis media") *OR* **TOPIC:** ("middle ear" NEAR/5 (infect* or inflam* or effus*)) *OR* **TOPIC:** (ome or aom) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years

Appendix 6. LILACS (BIREME) search strategy

tw:((mh:"Otitis Media" OR "Otitis Media" OR "Otite Média" OR mh:c09.218.705.663* OR "middle ear infection" OR "middle ear inflammation" OR "middle ear effusion" OR "serous otitis media" OR "OME" OR "AOM") AND (mh:"Adrenal cortex hormones" OR "Adrenal Cortex Hormones" OR corticoesteroides OR corticosteroides OR corticoides OR corticosteroides OR "Hormonas de la Corteza Suprarrenal" OR corticoid* OR corticoesteroides OR "Hormônios do Córtex Suprarrenal" OR mh:d06.472.040* OR corticosteroid* OR corticoid* OR steroid* OR glucocorticoid* OR esteroid* OR corticoid* OR mineralocorticoid* OR mh:pregnenediones OR pregnenodionas OR mh:d04.808.745.745.654* OR dicetopregnenos OR pregnenedionas OR pregnenedione* OR pregnenolone OR hydrocortisone OR hydroxypregnenolone OR tetrahydrocortisol OR cortodoxone OR "cortone acetate" OR cortisone OR corticosterone OR aristocort OR triamcinolone OR deltasone OR prednisone OR prednicot OR prednisolone OR "bubbli-pred" OR cotolone OR prelone OR pediapred OR "pms-prednisolone" OR paramethasone OR methylprednisolone OR baycadron OR dexamethasone OR decadron OR clobetasol OR beclomethasone OR betamethasone OR budesonide OR efcortesol OR hydrocortone OR "solu-cortef" OR cortef OR "A-Hydrocort" OR betnelan OR betnesol OR celestone OR deflazacort OR calcort OR medrone OR medrol OR "solu-medrone" OR "depo-medrone" OR "methylpred-DP" OR kenalog OR novolizer OR pulmicort OR symbicort OR "entocort EC" OR beclometasone OR aerobec OR asmabec OR beclazone OR becodisks OR becotide OR "clenil modulite" OR qvar OR becloforte OR cortisol OR mh:mineralocorticoids OR mineralocorticoid* OR mineralcorticoid* OR mh:aldosterone OR aldosterone OR aldosterona OR "florinef acetate" OR fludrocortisone)) AND (instance:"regional") AND (db:("LILACS"))

CONTRIBUTIONS OF AUTHORS

Respati W Ranakusuma (RR) drafted the protocol and contributed as a primary review author, selected studies for inclusion, extracted data, assessed the risk of bias, entered data into Review Manager 5, and carried out and interpreted the analysis.

Yupitri Pitoyo (YP) selected studies for inclusion, extracted data, and assessed the risk of bias.

Eka Dian Safitri (EDS) selected studies for inclusion, extracted data, and assessed the risk of bias.

Sarah Thorning (ST) developed and ran the search strategy, and obtained copies of studies.

Elaine M Beller (EMB) carried out and interpreted the analysis, contributed as the fourth review author for disagreements on methodological/statistical issues, and checked the correct use of grammar.

Sudigdo Sastroasmoro (SS) drafted the protocol, contributed to drafting the final review, and checked the correct use of grammar.

Chris B Del Mar (CDM) drafted the protocol and contributed as the fifth review author for disagreements on clinical issues (if needed), drafted the final review, and checked the correct use of grammar.

DECLARATIONS OF INTEREST

Respati W Ranakusuma: none known

Yupitri Pitoyo: none known

Eka Dian Safitri: none known

Sarah Thorning: none known

Elaine M Beller: her work on this review was supported by a grant from the National Health and Medical Research Council, Australia, to the Centre for Research in Evidence-Based Practice, Bond University

Sudigdo Sastroasmoro: none known

Chris B Del Mar: none known

CHAPTER 3: CURRENT MANAGEMENT OF CHILDREN WITH ACUTE OTITIS MEDIA: A FEASIBILITY SURVEY FOR A PRAGMATIC STUDY IN JAKARTA, DEPOK, AND BEKASI (STUDY 2)

Ranakusuma RW, McCullough AM, Beller EM, Del Mar CB, Safitri ED, Pitoyo Y, Widyaningsih W. Current management of children with acute otitis media: a feasibility survey for a pragmatic study.
Paediatrica Indonesiana. 2019;59(6):303-17.
DOI: 10.14238/pi59.6.2019.303-17.

3.1 SUMMARY

Our previous study (Study 1 – Cochrane review of systemic corticosteroids for acute otitis media [AOM] in children) showed that large, high-quality studies are required to address the effects of systemic corticosteroids for AOM.

Therefore, we planned to conduct a large quality, pragmatic, randomised, double-blinded, controlled trial (RCT) to address the effect of corticosteroids for AOM in children. Prior to this, we conducted a feasibility study (Study 2 – Current management of children with acute otitis media: a feasibility survey for a pragmatic study in Jakarta, Depok, and Bekasi) to identify the current management of children with AOM among general practitioners, Ear-Nose-Throat (ENT) specialists, and paediatricians who worked at primary care centres and hospitals in Jakarta, Depok, and Bekasi, Indonesia. This cross-sectional study also identified the number of children presenting with AOM in a week and the number of physicians who would participate in our planned pragmatic clinical trial. The study results were aimed at supporting the development of the strategy and methods for our protocol of a large, pragmatic RCT of oral corticosteroids for children with AOM in Indonesia, including the estimation of study duration, identification of potential obstacles and operational requirements in the study.

This study which consisted of responses from 352 clinicians (general practitioners=285, pediatricians=35, ENT specialists=32) retrieved from paper-based (N=339) and web-based questionnaires (N=13) showed that, given hypothetical clinical scenarios, most of the Indonesian physicians surveyed, particularly ENT specialists, would prescribe antibiotics for mild AOM. Slightly over half of the physicians, mostly paediatricians, would withhold antibiotic treatment and choose expectant observation. The number of participating physicians, who potentially would consider using corticosteroids, indicated that it would be feasible to conduct a clinical trial of oral corticosteroids for children with AOM in Indonesia. The following pages in this chapter include the results paper that has been published.

Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.59, No.6(2019). p. 303-17; doi: http://dx.doi.org/10.14238/pi59.6.2019.303-17

Original Article

Current management of children with acute otitis media: a feasibility survey for a pragmatic study

Respati W. Ranakusuma[1,2], Amanda R. McCullough[1], Elaine M. Beller[1], Christopher B. Del Mar[1], Eka D. Safitri[2], Yupitri Pitoyo[2], Widyaningsih[2]

Abstract

Background Acute otitis media (AOM) is a common self-limiting infection where antibiotics confer limited benefit. Other treatments, such as anti-inflammatory agents have been proposed as an alternative to antibiotics, but no high-quality clinical trials have tested this.

Objective To identify current AOM management practices among Indonesian clinicians. We also required this information for our proposed corticosteroids clinical trial for AOM.

Methods This cross-sectional study surveyed a convenience sample of general practitioners (GPs), pediatricians, and Ear-Nose-Throat (ENT) specialists in Jakarta, Depok, and Bekasi. We addressed their current AOM management practices and willingness to participate in a future trial on corticosteroids.

Results We distributed 2,694 questionnaires through conferences, primary care/hospital visits, and by mail-list group. Of 492 questionnaires received (response rate 18%), 352 were from eligible clinicians. Most clinicians diagnosed AOM by using an otoscope (64-91%). Tympanometry was used by a quarter of ENT specialists. Amoxicillin-clavulanate was the most common antibiotic for AOM, prescribed by pediatricians and ENT specialists, whilst most GPs prescribed amoxicillin. Clinical scenarios indicated most ENT specialists (88%) would prescribe antibiotics and most pediatricians (54%) would choose expectant observation by withholding antibiotics for mild AOM. Almost half of clinicians would consider using corticosteroids in a trial.

Conclusion Most clinicians would prescribe antibiotics for mild AOM. However, slightly over half of pediatricians would solely choose expectant observation. Adequate numbers of potential participating clinicians, who would consider using corticosteroids, make our proposed corticosteroids trial for AOM feasible. We found gaps between clinical practice and evidence requiring further investigation to improve AOM management in Indonesia. **[Paediatr Indones. 2019;59:303-17; doi: http://dx.doi.org/10.14238/pi59.6.2019.303-17]**.

Keywords: *otitis media; acute disease; anti-bacterial agents; health services; survey and questionnaires*

Antibiotics are commonly used for treating infectious diseases, including acute otitis media (AOM) in children.[1,2] International guidelines recommend expectant observation for mild AOM, with antibiotics only given for severe cases.[3,4] Although antibiotics are effective for AOM, their effects in improving pain and middle ear effusion are weak, they have potentially harmful side effects, and may lead to antibiotic resistance.[5,6] Currently, there are two conflicting Indonesian guidelines for AOM. One recommends antibiotics for both mild and severe AOM, while the other recommends antibiotics only for severe cases (although 'severe' is not clearly defined).[7,8] This potentially contributes to high use of antibiotics in the management of AOM in Indonesia, thereby

From The Institute for Evidence-Based Healthcare, Faculty of Health Sciences and Medicine, Bond University, Robina, Queensland, Australia[1], and Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo General Hospital, Universitas Indonesia Medical School, Jakarta, Indonesia.[2]

Corresponding author: Respati W. Ranakusuma. Institute for Evidence-Based Healthcare, Faculty of Health Sciences and Medicine, Bond University, 14 University Drive, Robina 4226, Queensland, Australia/ Clinical Epidemiology and Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital, Universitas Indonesia Medical School, H Building, 2nd level, Dr Cipto Mangunkusumo Hospital, Jl. Diponegoro 71, Jakarta 10430, Indonesia. Email: rranakus@bond.edu.au.

Submitted August 21, 2019. Accepted November 28 2019.

increasing the risk of antibiotic resistance and other side effects.[5,9,10] Finding alternative treatment options could be one way to mitigate the risk of antibiotic resistance. Theoretical considerations suggest that the anti-inflammatory effect of corticosteroids might reduce symptoms.[1] Conflicting evidence on the potential benefits requires a large randomized placebo-controlled trial (RCT) to test efficacy.[12,13] We plan to undertake a large RCT in Indonesia to further investigate this issue.

To date, there is no available data on the current AOM management for children in Indonesia. However, there have been several studies surveying the management of AOM in other countries.[14-16] A survey study in Turkey showed pediatricians were likely to prescribe antibiotics (60%) and analgesics (e.g., acetaminophen, ibuprofen) for children with AOM.[14] Surveys in India and Israel showed most ENT specialists prescribed antibiotics for AOM (62-98%). Analgesics and decongestants and/or antihistamines were also commonly prescribed. Most ENT specialists in India used an otoscope as a diagnostic tool for AOM, whilst a microscope was more preferable in Israel.[15,16]

We identified the current management, particularly with regards to prescribing antibiotics for AOM in three cities in Indonesia. This survey study was done to help us identify existing gaps between clinical practice and evidence in the management of AOM in Indonesia. Our survey was also designed to gauge clinicians' willingness to use corticosteroids in a future, randomized trial.

Methods

This study primarily aimed to identify the current management of AOM among clinicians. It also identified the feasibility of a proposed clinical trial to test corticosteroids for AOM in children. We conducted a cross-sectional study for our survey (April - August 2016). Our eligibility criteria were clinicians from three specialties (general practitioners, pediatricians, and ENT specialists) working in primary/secondary or tertiary healthcare facilities in Jakarta, Depok, and Bekasi, Indonesia. We established clinicians' specialties and email addresses from the national professional organizations of general practitioners (*Indonesian Medical Association*), pediatricians (*Indonesian Pediatric Society*), and ENT specialists (*Indonesian Otorhinolaryngology Head and Neck Surgery Society*). We then distributed paper-based questionnaires through workshops, conferences, primary healthcare and hospital visits. We also distributed electronic-based questionnaires through mailing lists of primary care clinician graduates from two medical schools in Jakarta (Universitas Indonesia and Universitas Pembangunan Nasional Veteran), identified by alumni and colleagues.

We invited participation in a 10-minute presentation at the following workshops and conferences: (i) The Indonesian National Committee for the Prevention and Management of Hearing Impairment and Deafness Meeting (20 May 2016), (ii) The Continuing Professional Development Program: The Comprehensive Management of Vestibulocochlear Disorders (20-21 May 2016), (iii) The Third Neurotology Update Management: Hearing and Vestibular Disorders in Children (21 May 2016), (iv) The Annual Scientific Meeting of the Indonesian Medical Association (27-29 May 2016), and (vi) The Second Jakarta Pediatric Respiratory Forum (29-30 May 2016). We distributed the questionnaires at the registration table on the first day of the workshops or conferences and collected the questionnaires at the end of the events.

We identified several primary healthcare clinics and hospitals located in Jakarta, Depok, and Bekasi that were conveniently accessible. We contacted the heads or directors of the appointed healthcare facilities and distributed the questionnaires to the emergency, pediatric, and otorhinolaryngology departments. We collected the questionnaires at most 4 weeks after their distribution, unless completed earlier.

Consenting clinicians typically completed the questionnaires in 10-20 minutes (**Appendix 1**). It had 3 sections: 1) current management of AOM in children, including diagnostic treatment items; 2) 3 clinical scenarios [(a.) a child aged < 2 years with mild AOM; (b.) a child aged ≥ 2 years with mild AOM; and (c.) an older child with recurrent and bilateral AOM] in which respondents were invited to describe their management (**Table 1**); and 3) a feasibility survey to identify the number of pediatric AOM patients and clinicians who might be willing to participate in our clinical trial on corticosteroids as an alternative treatment for AOM.

We did not formally determine a sample size estimate. We used convenience sampling based on ease of accessibility to the healthcare facilities and clinicians who attended workshops and conferences specifically for general practitioners, pediatricians, and ENT specialists. The results of this study are reported as the percentage of clinicians in each category of responses. We used Chi-square test to identify the differences between specialty groups using *IBM SPSS Statistics 23* software. All proportions are expressed from respondents who answered that question in the questionnaires.

This study protocol was reviewed and approved by the Ethics Committee of the Universitas Indonesia Medical School and Bond University Human Research Ethics Committee. We provided a paper- and electronic-based information sheet and consent form to all respondents. Consent was received in written form and the consent process was free of coercion. All information obtained from the respondents was treated as confidential.

Results

Of 2,694 questionnaires distributed, 492 were returned (response rate 18%). Of these, 445 (90%) participated in the survey, **Figure 1**. There were 352

Table 1. Clinical scenarios and their interpretation

Clinical scenarios	Interpretation/diagnosis	Treatment recommendation[3]
Clinical scenario 1: "A one-year old boy, accompanied by his mother, came to your practice with a complaint of pain in his left ear for one day. The pain was not severe. He has had a cold for the last two days with a mild fever. At the physical examination, he looked well and alert with temperature 37.8°C. At his ear, nose, and throat examination, there was mucous discharge on the nasal cavities, and his throat looked normal. An otoscopic examination showed redness and bulging tympanic membrane of the left ear."	A young child (aged < 2 years) with mild AOM	Expectant observation (begin antibiotics if child worsens or fails to improve within 48 to 72 hours of AOM onset) OR antibiotic therapy if close observation and follow-up cannot be ensured.
Clinical scenario 2: "A four-year old girl, accompanied by her parents, came to your practice with a complaint of pain in her right ear for one day. She has had a cold for the last four days. She had no fever. At the physical examination, the patient looked well and alert. At her ear, nose, and throat examination, there was serous secretion in the nasal cavities and her throat looked normal. An otoscopic examination showed redness and bulging tympanic membrane of the right ear."	An older child (aged ≥ 2 years) with mild AOM	Expectant observation (begin antibiotics if child worsens or fails to improve within 48 to 72 hours of AOM onset) OR antibiotic therapy if close observation and follow-up cannot be ensured.
Clinical scenario 3: "A five-year old girl, accompanied by her parents, came to your practice with a complaint of pain in her right ear for one day, followed by left ear this morning and she had a mild fever. She had experienced acute otitis media in her right ear one month ago. At the physical examination, the patient looked well and alert with temperature 36.8°C. At her ear, nose, and throat examination, there was minimal serous discharge in her nasal cavities and her throat looked normal. An otoscopic examination showed redness and bulging on both tympanic membranes."	An older child with recurrent bilateral AOM	Expectant observation (begin antibiotics if child worsens or fails to improve within 48 to 72 hours of AOM onset) OR antibiotic therapy if close observation and follow-up cannot be ensured. However, this guideline does not specify the need of antibiotics for recurrent AOM.

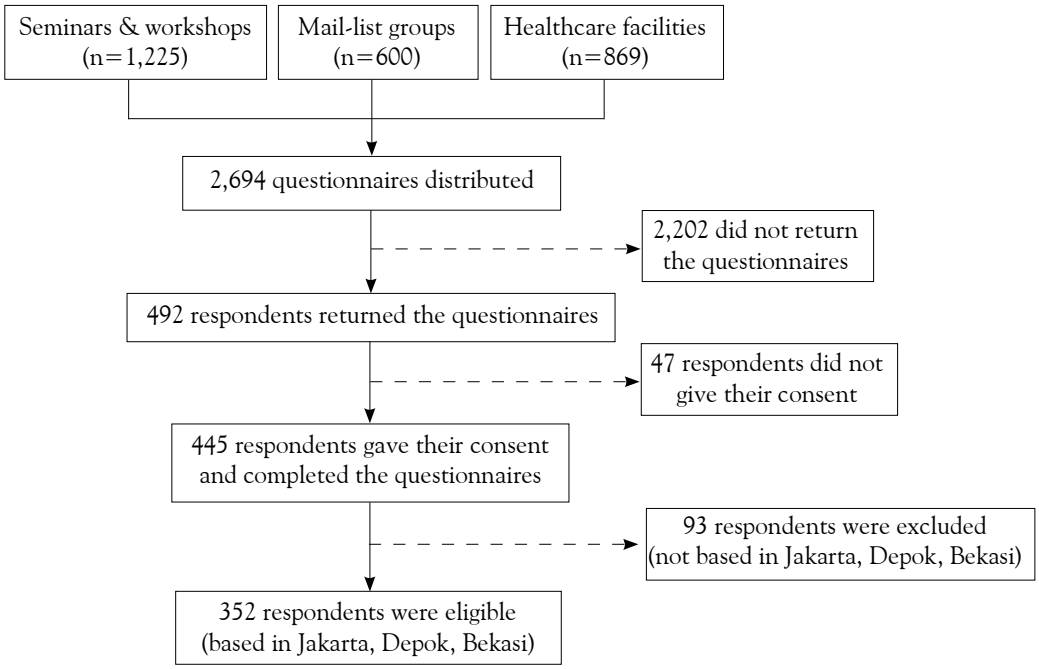


Figure 1. A flow diagram of study recruitment

clinicians who responded (general practitioners 81%, pediatricians 10%, and ENT specialists 9%) and they were based at primary/secondary (44%) and tertiary healthcare (54%) facilities (no response 2%) in Jakarta (82%), Depok (10%), and Bekasi (8%), our target regions. Most were young, <31 years (44%), and female (67%).

A total of 705 children with AOM visited 352 clinicians over a period of seven days prior to answering the questionnaire. Most clinicians had less than three AOM cases during this period (75%), and most of these children were between two and five years of age. ENT specialists had more AOM cases (three to five cases) per week compared to general practitioners and pediatricians.

Most clinicians diagnosed AOM by using an otoscope (64-91%) (**Table 2**). Three quarters of ENT specialists and 9% of general practitioners used an endoscope. Pediatricians did not use an endoscope. A quarter of ENT specialists, but very few pediatricians (3%) or general practitioners (1%), used tympanometry to identify middle ear effusion. Few clinicians (0-6%) used a pneumatic otoscope, audiometry (0-9%), or tympanocentesis (0-3%) to diagnose AOM.

Amoxicillin-clavulanate was the most common antibiotic prescribed by ENT specialists (58%), pediatricians (46%), and general practitioners (16%) (**Table 2**). Amoxicillin was the second most common antibiotic prescribed by general practitioners (43%) and pediatricians (37%), whilst ENT specialists prescribed cefixime as the second common antibiotics for AOM (23%). Azithromycin (0-13%), cefadroxil (0-9%), erythromycin (3%), ampicillin (0-3%), and cotrimoxazole (0-3%) were the least common antibiotics prescribed for AOM. General practitioners (66%) mostly prescribed amoxicillin for three to five days, whilst ENT specialists (56%) and pediatricians (54%) prescribed amoxicillin-clavulanate for more than five days.

The clinicians' treatment choices for the three clinical scenarios are shown in **Table 3**. In the first scenario, 88% of ENT specialists would prescribe antibiotics for AOM, followed by general practitioners (71%) and pediatricians (57%). More ENT specialists (44%) would prescribe corticosteroids when compared to other specialties (general practitioners 30%; pediatricians 23%). In the second scenario, 66% of ENT specialists would prescribe antibiotics, followed by general practitioners (52%) and pediatricians

Table 2. The common diagnostic tools and type of antibiotic prescribed among clinical specialties

Management	General practitioners* (Total=284), n(%)	ENT specialists (Total=32), n (%)	Pediatricians (Total=35), n(%)
Diagnostic examination			
Otoscope	183 (64)	29 (91)	24 (69)
Penlight/headlamp	159 (56)	9 (28)	20 (57)
Endoscope	25 (9)	24 (75)	0 (0)
Tympanometry	2 (1)	8 (25)	1 (3)
Tuning fork	10 (4)	4 (13)	0 (0)
Pneumatic otoscope	8 (3)	0 (0)	2 (6)
Tympanocentesis	1 (1)	3 (9)	0 (0)
Audiometry	4 (1)	1 (3)	0 (0)
Type of antibiotics**			
Amoxicillin-clavulanate	46 (16)	18 (58)	16 (46)
Amoxicillin	122 (43)	0 (0)	13 (37)
Cefixime	34 (12)	7 (23)	2 (6)
Azithromycin	4 (1)	4 (13)	0 (0)
Cefadroxil	26 (9)	0 (0)	0 (0)
Erythromycin	9 (3)	1 (3)	1 (3)
Ampicillin	4 (1)	0 (0)	1 (3)
Cotrimoxazole	8 (3)	0 (0)	0 (0)
Others	6 (2)	0 (0)	0 (0)
More than one	22 (8)†	1 (3)‡	2 (6)§

*One missing data in general practitioner group

**Total 281 general practitioners and 31 ENT specialists provided their options of antibiotic types for AOM

†General practitioners chose amoxicillin (77%, 17/22), followed by cefixime (32%, 6/22) and cefadroxil (32%, 6/22) in the multiple antibiotic prescription group.

‡ENT specialist did not mention any antibiotic by name but only reported 'depends on the condition'.

§Pediatricians chose cefixime (100%, 2/2), followed by amoxicillin (50%, 1/2) and amoxicillin-clavulanate (50%, 1/2) in the multiple antibiotic prescription group.

Table 3. Treatment options for three clinical scenarios among all specialties

Treatment options	Scenario 1 A young child (aged < 2 years) with mild AOM, n(%)				Scenario 2 An older child (aged ≥ 2 years) with mild AOM, n(%)				Scenario 3 An older child with recurrent bilateral AOM, n(%)			
	GP (n=283)	ENT (n=32)	PED (n=35)	Overall (n=350)	GP (n=280)	ENT (n=32)	PED (n=35)	Overall (n=347)	GP (n=279)	ENT (n=32)	PED (n=35)	Overall (n=346)
Expectant observation	140 (49)	8 (25)	20 (57)	168 (48)	136 (49)	9 (28)	17 (49)	162 (47)	132 (47)	8 (25)	16 (46)	156 (45)
Antibiotics	200 (71)	28 (88)	20 (57)	248 (71)	147 (52)	21 (66)	16 (46)	184 (53)	170 (61)	27 (84)	20 (57)	217 (63)
Corticosteroids	85 (30)	14 (44)	8 (23)	107 (31)	73 (26)	12 (37)	7 (20)	92 (27)	95 (34)	14 (44)	11 (31)	120 (35)
Acetaminophen	217 (77)	19 (59)	31 (89)	267 (76)	151 (54)	12 (37)	22 (63)	185 (53)	128 (46)	13 (41)	18 (51)	159 (46)
Ibuprofen	49 (17)	9 (28)	8 (23)	66 (19)	74 (26)	11 (34)	9 (26)	94 (27)	78 (28)	9 (28)	13 (37)	100 (29)
Decongestant/ antihistamine	201 (71)	29 (91)	24 (69)	254 (73)	222 (79)	30 (94)	29 (83)	281 (81)	145 (52)	29 (91)	21 (60)	195 (56)
Topical antibiotics	71 (25)	2 (6)	7 (20)	80 (23)	69 (25)	2 (6)	6 (17)	77 (22)	73 (26)	2 (6)	11 (31)	86 (25)
Topical analgesics	32 (11)	0 (0)	4 (11)	36 (10)	33 (12)	1 (3)	3 (9)	37 (11)	41 (15)	1 (3)	5 (14)	47 (14)
Physiotherapy	18 (6)	2 (6)	2 (6)	22 (6)	19 (7)	1 (3)	4 (11)	24 (7)	17 (6)	1 (3)	1 (3)	19 (6)

*Clinicians may choose more than one treatment option

(46%). Thirty-seven per cent of ENT specialists and only up to quarter of general practitioners (26%) and pediatricians (20%) would choose corticosteroids. In the third scenario, 84% of ENT specialists would prescribe antibiotics for AOM, followed by general practitioners (61%) and pediatricians (57%). Corticosteroids were more likely to be prescribed by ENT specialists (44%) compared to other specialties (general practitioners 34%, pediatricians 31%).

Clinicians would mostly prescribe acetaminophen (59-89%), decongestant/antihistamine (69-91%), and antibiotics (57-88%) for a young child with

mild AOM (Scenario 1) compared with other treatment (e.g., ibuprofen, corticosteroids, topical antibiotics, or topical analgesics). From all clinical scenarios, ENT specialists were more likely to prescribe corticosteroids (37-44%) and were less likely to choose expectant observation (25-28%), whereas pediatricians (46-57%) followed by general practitioners (47-49%) were more likely to choose expectant observation compared to ENT specialists. However, as clinicians may choose more than one treatment for the clinical scenario section, there were respondents who chose both expectant observation and antibiotics, which by definition should be mutually exclusive. By identifying those who solely chose expectant observation by withholding antibiotic treatment, pediatricians (43-54%) were still more likely to choose expectant observation compared to other specialties in all three scenarios. The rate of corticosteroid prescribed by pediatricians and general practitioners ranged from 20% to 34% across the three scenarios. A significant difference between specialty groups was identified in the first scenario, where pediatricians were significantly less likely to prescribe antibiotics (P=0.024) compared to general practitioners and ENT specialists, and in the third scenario where ENT specialists were more likely to prescribe antibiotics (P=0.026) compared to other specialties. With regards to prescribing antibiotics in each scenario among these specialties, ENT specialists were more likely to prescribe antibiotics compared to other specialties, particularly in the first and third scenarios.

As shown in **Figure 1**, of the 352 clinicians from Jakarta, Depok, and Bekasi, 171 respondents (49%) indicated their willingness to participate in our proposed clinical trial testing corticosteroids as an alternative treatment for AOM in children. Their characteristics were similar to the whole survey sample. They managed 443 children with AOM in a week. Most clinicians had less than three cases of AOM during this period (75%), with most of these children aged older than five years. ENT specialists had more AOM cases (three to five cases) per week compared to other specialties. These clinicians had a similar practice in the management of AOM and responses to clinical scenarios to the whole sample. Up to 44% of clinicians, mostly ENT specialists, would consider using corticosteroids in a trial.

Discussion

Our sample of clinicians who worked in Jakarta, Depok, and Bekasi, reported that they mostly diagnosed AOM by using an otoscope. Most general practitioners would prescribe amoxicillin for a short duration (3-5 days), whilst ENT specialists and pediatricians were more likely to prescribe amoxicillin-clavulanate for a longer duration. Clinical scenario results showed there was a high rate of antibiotics prescribed for mild AOM. Up to 44% of clinicians would have prescribed corticosteroids for children with AOM. Both corticosteroids and antibiotics were mostly prescribed by ENT specialists in the scenarios. There is no clear justification for a high rate of antibiotic prescribing by ENT specialists. As ENT specialists saw more patients with AOM in the sampled week compared to other specialties, their contribution to antibiotic prescribing would be higher and, therefore, the risks correlated with antibiotic use, such as adverse events and antibiotic resistance would be increased.[5,9,10] Another reason for this high use was due to potential complications following AOM, such as spontaneous perforation of the tympanic membrane (15%) and persistent middle ear effusion (25%).[17,18] High rates of antibiotic prescribing by general practitioners might be influenced by the Indonesian practice guideline recommending antibiotics for both mild and severe AOM.[7] Interestingly, we found pediatricians were less likely to prescribe antibiotics for all scenarios in the study. One potential justification for this was that international pediatrics practice guidelines do not recommend antibiotics for common colds and only recommend antibiotics for AOM with high risks (e.g., children with severe signs and symptoms, children < 2 years with bilateral AOM, or tympanic membrane perforation).[3,4,19] Corticosteroids and antibiotics were more likely to be prescribed for AOM in younger children and recurrent bilateral AOM. These are not entirely in accordance with the guidelines, as corticosteroids have not been recommended by any guidelines. The guidelines only recommend the use of antibiotics for children under two years of age with bilateral AOM, whilst our scenario was a case of unilateral AOM.[3]

Unfortunately, few clinicians (<7%, and none of the ENT specialists) used pneumatic otoscopy, which enables the assessment of tympanic membrane

mobility.[3,20] A systematic review showed that a pneumatic otoscope performed by a skilled clinician can accurately diagnose AOM with high predictive values. It can replace tympanometry as one diagnostic tool for AOM, as the pneumatic otoscope is a more affordable.[21] Our clinical scenarios demonstrated that most clinicians would prescribe antibiotics over expectant observation for mild AOM. Evidence recommends expectant observation with sufficient pain management for mild AOM.[3-5,9] Only 30% of AOM cases are severe and require antibiotic treatment.[5,9] However, antibiotic prescribing rates for AOM in developed and developing countries are still relatively high. In terms of data from general practices in Australia over five years, 89% of new AOM cases were managed with antibiotics.[22] Meanwhile, data from the *National Ambulatory Medical Care Survey* (NAMCS) demonstrated 83.1% of children with isolated AOM were managed with antibiotics.[23] Our study demonstrated that up to 88% of clinicians would prescribe antibiotics for a mild case of AOM. *The Indonesian Practice Guideline* recommends antibiotics for both mild and severe AOM, which may influence the high rate of antibiotic prescribing for AOM in Indonesia.[7] A red and bulging tympanic membrane could be the other reason for antibiotic treatment in all scenarios. However, the sign of red tympanic membrane is not sensitive (18%), with a low likelihood ratio for a positive result of 1.1, regardless of its high specificity (84%). Although a bulging tympanic membrane will help make the diagnosis, it requires the combination of cloudiness and the impaired mobility of the tympanic membrane to robustly diagnose AOM.[20]

Recurrent AOM was the second most common reason for antibiotic prescribing in this study. This is defined as "the occurrence of 3 or more episodes of AOM in a 6-month period or the occurrence of 4 or more episodes of AOM in a 12-month period that includes at least 1 episode in the preceding 6 months".[3] *The American Academy of Pediatrics Clinical Practice Guideline* does not recommend the use of prophylactic antibiotics for reducing the number of episodes of AOM in recurrent AOM cases, and yet tympanostomy tubes should be offered.[3] Systematic reviews showed that recurrent AOM is not included as one indicator for antibiotic treatment in the management of AOM.[5,9] However, *The 2014 New South Wales Guideline* includes recurrent AOM into the high-risk middle ear infection category, which requires immediate antibiotic treatment. [24]

The high rate of antibiotic prescribing in AOM indicates the need for alternative non-antibiotic treatment for AOM. We propose to test corticosteroids for AOM. Inflammation has been indicated as an important mechanism in AOM, despite the complexity of the pathophysiology of AOM. This involves both cellular and chemical mediators (e.g., cytokines, chemokines, mast cells, and leukotrienes). Corticosteroids could act as an anti-inflammatory agent, particularly in the middle ear,[12] and therefore reduce pain. Insufficient evidence of the effects of corticosteroids for AOM requires a large, high-quality, clinical trial to evaluate corticosteroid efficacy to improve the resolution of AOM, as a monotherapy in mild cases or as an addition to antibiotic therapy in severe cases.[12]

Our feasibility survey demonstrated that there were 171 clinicians who were willing to participate in our clinical trial and who saw 443 children with AOM in a week. They also had similar practices in the management of AOM and responses to clinical scenarios to the whole sample. This study also demonstrated that a sufficient number of clinicians would consider using corticosteroids for AOM. This finding was surprising; however, this high rate could be primed by clinicians' knowledge of the nature of the upcoming clinical trial, which had been provided in the consent form and at the conference presentations prior to the completion of the questionnaires. As nearly half of the clinicians were interested in participating in our trial, it is feasible to conduct a clinical trial on corticosteroids for AOM in children in Indonesia, according to the pre-specified timeline (12 months, including a three-month follow-up).

We believe this the first survey of current practices of clinicians in the management of pediatric AOM in Indonesia, which was the strength of this study. We identified clinicians' preferred treatment options, particularly in choosing corticosteroids, expectant observation, and antibiotics. However, this study also had several limitations, including the low response rate, unclear definition of 'observation for 48 to 72 hours' as one answer option in the clinical scenario, and a narrow study-site coverage. We tried several recruitment strategies to increase the response rate, however, as participation was voluntary, it was

the respondents' decision to consent and participate in this survey study. There is no gold standard for an acceptable minimum survey response rate, however, a response rate of at least 70% is desirable.[25] Nonetheless, surveys involving voluntary clinicians mostly have low response rates (< 30%).[25] There are several factors that influence the willingness of clinicians to participate in a survey study, such as concerns about disruption of their practice, time, and relevance of the survey topic.[26] A review assessing survey response rates of general practitioners from published primary care journals demonstrated that the mean response rate was 61% (95% confidence interval 59% to 63%).[27] A cross-sectional study comparing the response rates between postal and online survey of general practitioners across Australia showed low response rates for both (12.4% and < 0.1%, respectively), which were similar to our study.[28] Several contributing factors were workload of the general practitioners, increasing number of other similar surveys, and no incentives for participating general practitioners. A systematic review identifying strategies to improve response rates on postal and electronic questionnaires demonstrated that the responses were likely almost doubled when there were monetary/non-monetary incentives, recorded delivery, shorter questionnaires, and interesting survey topics.[29] We did not have any funding to provide incentives. Other weakness of the study was Wwe did not clearly define the answer option of 'observation for 48 to 72 hours' in the clinical scenarios. The option for observation for 48 to 72 hours was meant for clinicians who would choose to closely observe the AOM patients without antibiotics treatment for 48 to 72 hours. Without a clear definition, clinicians who would prescribe antibiotics, may also choose observation to see the effect of antibiotics. This would limit us to precisely identify the proportion of clinicians who would solely choose observation by withholding antibiotic treatment. As the last study weakness, this study only covered three adjacent cities in two provinces (Jakarta and a small part of West Java), which certainly does not represent the current management practice of AOM in Indonesia in general (total provinces in Indonesia is 34). To generalize these findings to the rest of Indonesia requires a national scale study that includes multiple cities (rural and urban) representing each province in Indonesia, supported by the *Ministry of Health, Republic of Indonesia.* Given that the self-reported nature of our study is a further limitation, a national study should collect objective data on the actual number of AOM cases (including diagnosis and treatment) from primary care or hospital patient databases. However, our purpose was to survey likely practice and participation in a proposed trial.

There is still a high rate of antibiotic prescribing among Indonesian clinicians for children with AOM. Although it has not been recommended in the guidelines, clinicians would consider using corticosteroids for AOM. Given nearly half of clinicians were interested in participating in a future trial on corticosteroids, our proposed trial is feasible. This survey demonstrated existing gaps in the management of AOM between clinical practice and evidence. It is crucial to translate scientific evidence to clinical practice to improve the quality of the AOM management in children, particularly in Indonesia, by promoting an accurate and affordable diagnostic tool for AOM, such as a pneumatic otoscope, as well as by prescribing antibiotics only for severe AOM, and offering an observation under adequate pain management for mild cases. Therefore, further investigation is required to identify other contributing factors to be able to tackle this problem comprehensively.

Conflicts of Interest

Dr. Ranakusuma (RR) reports grants from The Australian Commonwealth Government, during the conduction of the study.
Dr. McCullough (AMC) reports grants from Advance Queensland Women's Academic Fund - Maternity, an Early Career Researcher award from Bond University, and was named the BUPA Health Foundation Emerging Researcher 2017 during the conduction of the study. She runs two businesses that undertake work outside the submitted work: Not Just Mum and Amanda McCullough Consulting.
Dr. Beller (EMB) reports grants from The Centre for Research Excellence in Minimising Antibiotic Resistance in the Community (CRE-MARC) Grant, National Health & Medical Research Council (NHMRC grants), Australia, during the conduction of the study.

Dr. Del Mar (CDM) reports grants from The Centre for Research Excellence in Minimising Antibiotic Resistance in the Community (CRE-MARC) Grant, NHMRC (Australia) (NHMRC grants), grants from Australian Commission for safety and Quality in Health Care (ACSQHC) (consultancy), personal fees from BUPA (UK) (consultancy), personal fees from Book royalties (Elsevier; Wiley), grants from Cochrane ARI Group, (NHMRC grant), during the conduction of the study.
Dr. Pitoyo (YP), Dr Safitri (EDS), Widyaningsih (WW) have nothing to disclose.

Acknowledgments

We thank Professor DR. Dr. Sudigdo Sastroasmoro, Sp.A(K), Professor DR. Dr. Jenny Bashiruddin, Sp.THT-KL(K), and Siti Rizny Fitriani Saldi, Pharm, MSc for their support and feedback in the development of the protocol and the implementation of the study. We also thank Professor Paul Glasziou, FRACGP, PhD (Director of Centre for Research in Evidence-Based Practice, Bond University, Queensland, Australia) and Professor DR. Dr. Siti Setiati, Sp.PD-KGer, M.Epid (Director of Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital/Universitas Indonesia Medical School) or their support in the preparation and implementation of this study; Dr. Brastho Bramantyo, Sp.THT-KL (Chair of Continuing Professional Development Program and The 3rd Neurotology Update Management: Hearing and vestibular Disorders in Children Committee), Dr. Damayanti Soetjipto, Sp.THT-KL(K) (Chair of the Indonesian National Committee for the Prevention and Management of Hearing Impairment and Deafness), Dr. Darmawan Budi S, Sp.A(K) (Chair of The 2nd Jakarta Pediatric Respiratory Forum Committee), and Dr. Fazilet Soeprapto, MPH (The Annual Scientific Meeting of the Indonesian Medical Association) for letting us distribute the questionnaires in these conferences; Cameron Lydster, Bond University, for assistance with proofreading; Dr. Novia R. Tampubolon and Ms. Vonny V. Soeloe for their assistance in planning and conducting the study; and all the clinicians who participated in the survey.

Funding acknowledgment

This work research was supported by an Australian Government Research Training Program Scholarship and the Australian National Health and Medical Research Council [NHMRC Grant Number 1044904] as part of the Centre for Research Excellence in Minimising Antibiotic Resistance for Acute Respiratory Infections/CREMARA, received by CDM and EMB [https://researchdata.ands.org.au/centre-research-excellence-infectionscremara/111700]. These funding bodies had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and material

The datasets generated and/or analyzed during the current study are available in the Bond University Research repository, [https://research.bond.edu.au/en/publications/current-management-of-children-with-acute-otitis-media-by-indones].

References

1. Pettigrew MM, Gent JF, Pyles RB, Miller AL, Nokso-Koivisto J, Chonmaitree T. Viral-bacterial interactions and risk of acute otitis media complicating upper respiratory tract infection. J Clin Microbiol. 2011;49:3750-5.
2. Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, *et al*. Viral upper respiratory tract infection and otitis media complication in young children. Clin Infect Dis. 2008;46:815-23.
3. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, *et al*. The diagnosis and management of acute otitis media. Pediatrics. 2013;131: e964-99.
4. South Australian Child Health Clinical Network. South Australian Paediatric Practice Guidelines: acute otitis media in children. South Australia: SA Health; 2014. ISBN No.: 978-1-74243-551-0. p.1-10.
5. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2015;8:CD000219.
6. Bakhit M, Hoffman T, Scott AM, Beller E, Rathbone J, Del Mar C. Resistance decay in individuals after antibiotic exposure in primary care: a systematic review and meta-analysis. BMC Med. 2018;16:126.
7. Kementrian Kesehatan Republik Indonesia. Panduan praktik klinis bagi dokter di fasilitas pelayanan kesehatan primer. Jakarta: Menteri Kesehatan Republik Indonesia; 2014. Peraturan Menteri Kesehatan Republik Nomor 5 Tahun 2014. p.176-80.

8. Kelompok Studi Otologi Perhimpunan Dokter Spesialis THT-KL Indonesia (PERHATI-KL). Guideline penyakit THT-KL di Indonesia. Jakarta: Perhimpunan Dokter Spesialis THT-KL Indonesia; 2007. p.55.
9. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368:1429-35.
10. Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ. 2015;187:E21-31.
11. Juhn SK, Jung MK, Hoffman MD, Drew BR, Preciado DA, Sausen NJ, *et al.* The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. Clin Exp Otorhinolaryngol. 2008;1:117-38.
12. Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, *et al*. Systemic corticosteroids for acute otitis media in children. Cochrane Database Syst Rev. 2018;3:CD012289.
13. Ruohola A, Heikkinen T, Jero J, Puhakka T, Juvén T, Närkiö-Mäkelä M, *et al.* Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes. J Pediatr. 1999;134:459-63.
14. Büyükcam Y, Kara A, Bedir T, Gülhan B, Özdemir H, Sütçü M, *et al.* Pediatricians' attitudes in management of acute otitis media and ear pain in Turkey. Int J Pediatr Otorhinolaryngol. 2018;107:14-20.
15. D'silva L, Parikh R, Nanivadekar A, Joglekar S. A questionnaire-based survey of Indian ENT surgeons to estimate clinic prevalence of acute otitis media, diagnostic practices, and management strategies. Indian J Otolaryngol Head Neck Surg. 2013;65(Suppl 3):S575-81.
16. Marom T, Bobrow M, Eviatar E, Oron Y, Ovnat Tamir S. Adherence to acute otitis media diagnosis and treatment guidelines among Israeli otolaryngologists. Int J Pediatr Otorhinolaryngol. 2017;95:63-8.
17. Neumark T, Ekblom M, Brudin L, Groth A, Eliasson I, Molstad S, *et al.* Spontaneously draining acute otitis media in children: an observational study of clinical findings, microbiology and clinical course. Scand J Infect Dis. 2011;43:891-8.
18. Gribben B, Salkeld LJ, Hoare S, Jones HF. The incidence of acute otitis media in New Zealand children under five years of age in the primary care setting. J Prim Health Care. 2012;4:205-12.
19. Hersh AL, Jackson MA, Hicks LA, Committee on Infectious Diseases. Principal of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. Pediatrics. 2013;132:1146-54.
20. Pirozzo S, Del Mar C. Chapter 27. Otitis media. In: Moyer VA, editor. Evidence based paediatrics and child health. London: BMJ Books; 2000. p. 238-47.
21. Blomgren K, Pitkäranta A. Current challenges in diagnosis of acute otitis media. Int J Pediatr Otorhinolaryngol. 2005;69:295-9.
22. McCullough AR, Pollack AJ, Plejdrup Hansen M, Glasziou PP, Looke DF, *et al.* Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. Med J Aust. 2017;207:65-9.
23. Sidell D, Shapiro NL, Bhattacharyya N. Demographic influences on antibiotic prescribing for pediatric acute otitis media. Otolaryngol Head Neck Surg. 2012;146:653-8.
24. New South Wales Ministry of Health. Infants and children, otitis media: Acute management of sore ear. Clinical Practice Guidelines. Sydney: NSW Ministry of Health; 2014. Document number GL2014_023. p.1-17. [cited 2019 June 27]. Available from: https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2014_023.pdf.
25. Bonevski B, Magin P, Horton G, Foster M, Girgis A. Response rates in GP surveys - trialling two recruitment strategies. Aust Fam Physician. 2011;40:427-30.
26. Pit SW, Vo T, Pyakurel S. The effectiveness of recruitment strategies on general practitioner's survey response rates - a systematic review. BMC Med Res Methodol. 2014;14:76.
27. Creavin ST, Creavin AL, Mallen CD. Do GPs respond to postal questionnaire surveys? A comprehensive review of primary care literature. Fam Pract. 2011;28:461-7.
28. Crouch S, Robinson P, Pitts M. A comparison of general practitioner response rates to electronic and postal surveys in the setting of the National STI Prevention Program. Aust N Z J Public Health. 2011;35:187-9.
29. Edwards PJ, Roberts I, Clarke MJ, DiGuiseppi C, Wentz R, Kwan I, *et al.* Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev. 2009;3:MR000008.

Appendix 1. Questionnaires of the study

QUESTIONNAIRE: THE MANAGEMENT OF ACUTE OTITIS MEDIA IN CHILDREN IN DKI JAKARTA, DEPOK, AND BEKASI	
THANK YOU FOR YOUR TIME AND PARTICIPATION IN FILLING THIS QUESTIONNAIRE. PLEASE TICK (V) YOUR ANSWER	
1	**INCIDENCE, ATTITUDE, AND BEHAVIOUR**
1.1	In your personal practice, how many cases of acute otitis media in children did you see in the past 7 (seven) days? Answer: ..... (.....) cases
1.2	Can you estimate the percentage for each age group of AOM patients who came to your personal practice in the past one month? Answer: .....% 0 to ≤ 2 year old .....% 2 to 5 year old .....% ≥ 5 year old
1.3	The diagnosis of acute otitis media was established using tests mentioned below *(you may choose more than one)* Answer: O Clinical history O Visualization of tympanic membrane using a penlight/ headlight O Visualization of tympanic membrane using an otoscope O Visualization of tympanic membrane using a pneumatic otoscope (using Siegel) O Visualization of tympanic membrane using ear endoscope / microscope O Tuning fork O Pure tone audiometry O Tympanometry / impedance audiometry O Tympanocentesis O Others: .....
1.4	What is the most common antibiotic you give for acute otitis media cases in children (*please choose only one of the following*): Answer: O Amoxicillin O Ampicillin O Cefixime O Cefadroxil O Erythromycin O Azitromycin O Amoxicillin-clavulanate O Cotrimoxazole O Others: .....
1.5	What is the most common duration of antibiotics you give for acute otitis media in children Answer: ..... days
2	**CASE SCENARIO (*there is no 'RIGHT' or 'WRONG' answer*)**
2.1	**CASE-1** A one-year old boy, accompanied by his mother, came to your practice with a complaint of pain in his left ear for one day. The pain was not severe. He has had a cold for the last two days with a mild fever. At the physical examination, he looked well and alert with temperature 37.8°C. At his ear, nose, and throat examination,

	there was mucous discharge on the nasal cavities, and his throat looked normal. An otoscopic examination showed redness and bulging tympanic membrane of the left ear.	
	Question:	What the best management for the patient above? *(you may choose more than one)*
	Answer:	O Observation for 48 – 72 hours O Decongestant and/or anti-histamine O Antibiotics O Paracetamol O Ibuprofen OR other anti-inflammatory drugs (NSAID) O Corticosteroids O Antibiotic ear drop O Analgesics ear drop O Physical therapy with *(you may have more than one answer)* O Nebulizer O Diathermy O Laser O Others .....
2.2	CASE-2 A four-year old girl, accompanied by her parents, came to your practice with a complaint of pain in her right ear for one day. She has had a cold for the last four days. She had no fever. At the physical examination, the patient looked well and alert. At her ear, nose, and throat examination, there was serous secretion in the nasal cavities and her throat looked normal. An otoscopic examination showed redness and bulging tympanic membrane of the right ear.	
	Question:	What the best management for the patient above? *(you may choose more than one)*
	Answer:	O Observation for 48 – 72 hours O Decongestant and/or anti-histamine O Antibiotics O Paracetamol O Ibuprofen OR other anti-inflammatory drugs (NSAID) O Corticosteroids O Antibiotic ear drop O Analgesics ear drop O Physical therapy with *(you may have more than one answer)* O Nebulizer O Diathermy O Laser O Others .....
2.3	CASE-3 A five-year old girl, accompanied by her parents, came to your practice with a complaint of pain in her right ear for one day, followed by left ear this morning and she had a mild fever. She had experienced acute otitis media in her right ear one month ago. At the physical examination, the patient looked well and alert with temperature 36.8°C. At her ear, nose, and throat examination, there was minimal serous discharge in her nasal cavities and her throat looked normal. An otoscopic examination showed redness and bulging on both tympanic membranes.	
	Question:	What the best management for the patient above? *(you may choose more than one)*

	Answer:	O Observation for 48 – 72 hours O Decongestant and/or anti-histamine O Antibiotics O Paracetamol O Ibuprofen OR other anti-inflammatory drugs (NSAID) O Corticosteroids O Antibiotic ear drop O Analgesics ear drop O Physical therapy with *(you may have more than one answer)* O Nebulizer O Diathermy O Laser O Others .....
3	**BIODATA**	
3.1	Doctor specialty	
	Answer:	O General practitioner O Paediatrician O Otorhinolaryngologist
3.2	Type of practice	
	Answer:	O Primary healthcare O Private or multi doctor clinic O Public hospital O Private hospital
3.3	City of practice	
	Answer:	O DKI Jakarta O Depok O Bekasi O Others: .....
3.4	Age	
	Answer:	O ≤ 30 years old O 31 – 40 years old O 41 – 50 years old O 51 – 60 years old O 61 – 70 years old O > 70 years old
3.5	Gender	
	Answer:	O Male O Female
4	**PARTICIPATION ON THE FUTURE CLINICAL RESEARCH ON THE MANAGEMENT OF ACUTE OTITIS MEDIA IN CHILDREN**	
	Research summary Antibiotic resistance has been emerging as a global public health problem. Antibiotics have been prescribed for almost 50% cases of acute respiratory infections (ARIs) in primary healthcare centres. As those cases are mostly self-limited diseases and caused by viruses, antibiotics have little or no clinical benefits. As part of a common complication of viral ARIs, acute otitis media (AOM) is mostly found in children and is a key reason for antibiotic prescription.	

	Other strategy than antimicrobial treatment is needed due to the progression into recurrent and persistent AOM. Corticosteroids have an important role as an anti-inflammatory agent. A recent study has shown the use of oral corticosteroid as an additional treatment with antibiotics in cases of AOM with discharge through tympanostomy tubes shortened the duration of otorrhea. There are few small trials on the use of corticosteroids also as an additional treatment of antibiotics in AOM in children and the results of its benefits were varied. Therefore, we plan to conduct a large, well-conducted clinical trial in order to assess the effectiveness of corticosteroid for the treatment of AOM in children	
	After reading this summary of the future research of "Corticosteroid as an alternative treatment for acute otitis media in children" that will be held on February 2017 to February 2018, I would be interested to be involved in this future research	
	Answer:	O NO, I am not interested to be involved O YES, I am interested to be involved. Please complete the following questionnaire below.
Thank you for your time in completing the survey *For those who are interested in participating in our future clinical research of "Corticosteroid as an alternative treatment for acute otitis media in children", please complete your contact details and other information below.*		
5	**BIODATA**	
5.1	Name and title	.....
5.2	Home address	....
5.3	Email address	.....
5.4	Telephone no. Mobile no.	....
5.5	Contact preference	O Telephone O SMS / Whatsapp O Email
5.6	Name/type of practice	....
5.7	Working since	..... (month) / ..... (year)
5.8	Practice address	....
5.9	Practice phone no. Fax no.	....
5.10	Is there an otoscope in your practice?	
	Answer:	O Yes O No
5.11	Is there a pneumatic otoscope (with Siegel) in your practice?	
	Answer:	O Yes O No
5.12	Is there a Tympanometer in your practice?	
	Answer:	O Yes O No
5.13	Is there a Pharmacy in your practice?	
	Answer:	O Yes

		O No. Where can your patient can get their medication? .....
6	**CURRENT EMPLOYMENT**	
	Do you work in other practice or institution/organization?	
	Answer:	O No O Yes. Please answer the following questions below
6.1	Name of other practice (primary health centre/clinic/ hospital)	.....
6.1.1	Working since	..... (month) / ..... (year)
6.1.2	Practice address	.....
6.1.3	Practice telephone no. Fax no.	....
6.2	Name of other employment (lecturer/researcher/scientific writer)	.....
6.2.1	Working since	..... (month) / ..... (year)
6.2.2	Address	.....
6.2.3	Practice telephone no. Fax no.	....
7	**EDUCATION**	
7.1	Bachelor	Faculty of Medicine University of ..... City ..... Completion year .....
7.2	Specialist	Faculty of Medicine University of ..... City ..... Completion year .....
7.3	Others (PhD, Masters)	Faculty of ..... University of ..... City ..... Completion year .....
7.4	Internship (PTT)	O No O Yes. Please answer the following questions below: Completion year ..... Duration ..... year
*** *Thank you for your interest. We will contact you for further information* ***		

Please return this questionnaire to:
Prof. Dr. dr. SS / dr. RWR
Address: **********
or contact us at +62********

CHAPTER 4: ORAL PREDNISOLONE FOR ACUTE OTITIS MEDIA IN CHILDREN: A PILOT PRAGMATIC, RANDOMISED, OPEN-LABEL, CONTROLLED STUDY (STUDY 3)

Ranakusuma RW, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, Beller EM. Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study (OPAL study).
Pilot and Feasibility Studies. 2018;4:146.
DOI: 10.1186/s40814-018-0337-x.
https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-018-0337-x

Ranakusuma RW, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, Beller EM. Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, controlled study (OPAL study). *Pre-print version.*

4.1 SUMMARY

Our second study (Study 2 – Current management of children with acute otitis media: a feasibility survey for a pragmatic study in Jakarta, Depok, and Bekasi) showed it was feasible to conduct a large clinical trial testing oral corticosteroids for children with acute otitis media (AOM). It was crucial to pilot our pre-specified procedures and measures in a smaller scale study or a pilot study (Study 3 – A pilot pragmatic, randomised, open-label, controlled study of oral prednisolone for acute otitis media in children). Due to budget constraints, our pilot study did not use placebo as a control, which made this study a single-blind study, instead of double-blind. This pilot study carried out all planned procedures in the protocol of the main study, identified potential obstacles from participating practitioners and study participants, and verified the sample size of the main study.

We also conducted a mechanistic sub-study (tympanometry sub-study) as part of the pilot study to identify whether oral corticosteroids could improve middle ear effusion (MEE) and whether these improvements correlated with the resolution of pain and other AOM-related symptoms.

Our pilot study showed that it was feasible to implement all pre-specified procedures and measures in the main study by all participating healthcare personnel, study participants, and their parents. We will need a smaller sample size compared to our original sample size calculation. We found that oral prednisolone may potentially reduce the pain intensity at Day 3, and improve tympanometry at Day 7, but may cause drowsiness. The pilot study confirms the importance of conducting our main study, which is a large, pragmatic, randomised, double-blind, placebo-controlled study. This chapter consists of the published protocol paper for the pilot study, and the results paper which has been submitted for publication and is under review.

Ranakusuma et al. Pilot and Feasibility Studies (2018) 4:146
https://doi.org/10.1186/s40814-018-0337-x

Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study (OPAL study)

Respati W. Ranakusuma[1,2*], Amanda R. McCullough[1], Eka D. Safitri[2], Yupitri Pitoyo[2], Widyaningsih[2], Christopher B. Del Mar[1] and Elaine M. Beller[1]

Abstract

Background: Acute otitis media (AOM) is an acute inflammation of the middle ear commonly found in children, for which antibiotics are frequently prescribed. However, antibiotics are beneficial for only one third of AOM cases, and then, with only modest benefit. Since antibiotic use leads to risk of side effects and resistance, effective alternative treatments are required. Corticosteroids are a candidate because of their anti-inflammatory effects, although evidence of their efficacy and harms is insufficient. Accordingly, we plan a large, rigorous clinical trial to test this. Initially, we will test pre-specified methods and procedures (including the overall process, resources, management, and scientific components) in a pilot study of corticosteroids for AOM, which will inform a future, definitive trial.

Methods: This is a pilot pragmatic, randomised, open-label, single-blind, controlled study of corticosteroids as either monotherapy or an addition to antibiotics in 60 children aged 6 months to 12 years with AOM in two cities (Jakarta and Bekasi) in Indonesia. We will randomise eligible children to prednisolone or control. We will also stratify by disease severity and randomise those with mild AOM to expectant observation plus prednisolone or observation alone and those with severe AOM to prednisolone plus antibiotic or antibiotic alone. Our outcomes are to determine (1) recruitment rates, (2) the success of the study procedures, (3) the ability to measure planned outcomes of the proposed main study, (4) the compliance to study visits and study medication, and (5) verification of the sample size calculation for the main study. We will also assess middle ear effusion using tympanometry as part of a mechanistic sub-study.

Discussion: This study will test all procedures in preparation for the main study, including several potential obstacles and challenges from the perspective of participating physicians, nurses, pharmacists, and the parents of eligible children. This information will be useful for developing strategies to overcome practical and procedural issues. This study may also provide information about the effects of corticosteroids on middle ear effusion in AOM.

Trial registration: Study registry number: ACTRN12618000049279. Name of registry: the Australian New Zealand Clinical Trials Registry (ANZCTR). Date of registration: 16 January 2018.

Keywords: Acute otitis media, Antibiotics, Corticosteroids, Middle ear effusion, Mechanistic sub-study, Tympanometry, Trial protocol

* Correspondence: rranakus@bond.edu.au
[1]Centre for Research in Evidence-Based Practice Faculty of Health Sciences and Medicine Bond University, 14 University Drive, Robina 4226, Queensland, Australia
[2]Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo General Hospital – Faculty of Medicine Universitas Indonesia, Diponegoro 71, Jakarta 10430, Indonesia

Background

Antibiotic resistance is a major global health threat, which is mostly driven by antibiotic prescribing [1]. Antibiotics are commonly prescribed in primary care for acute respiratory infections, including acute otitis media [2–4]. Acute otitis media (AOM) is an inflammation of the middle ear commonly found in children [5]. Approximately 75% of children experience AOM before the age of five [6]. Recurrent AOM, defined as three or more AOM episodes in the past 6 months or four or more episodes in the past 12 months with at least one episode in the past 6 months, occurs in 24% of American children up to aged three [5, 7]. In Europe, 2% of children under six have had three or more episodes of AOM the previous year [6].

In the management of AOM, expectant observation with pain management is commonly recommended for children with mild AOM (e.g. mild ear pain, fever < 39 °C) who can be reliably followed up [5]. Those with severe symptoms, bilateral AOM in young age children, or with perforated ear drums are more likely to benefit from antibiotics [5, 8]. The option of using antibiotics must be balanced against common adverse effects (e.g. vomiting, diarrhoea, or rash) [9, 10]. In Australian general practice, 89% of new AOM cases are managed with antibiotics [11]. Similarly, in Indonesia, our survey study demonstrated about 88% of physicians would prescribe antibiotics for children with mild AOM. Indonesian practice guidelines on the criteria for antibiotic use for AOM are vague [12, 13].

Alternative treatments have been proposed for treating AOM, including herbal preparations, decongestants, and corticosteroids [14–16]. However, the evidence for these is too weak to be recommended in clinical practice. The anti-inflammatory effect of corticosteroids suggests it could be a viable treatment alternative for AOM [17]. Moreover, corticosteroids are effective additions to treatment for other, more serious acute respiratory infections, including pneumonia [18] and bacterial meningitis [19]. However, there is insufficient evidence of efficacy and harms for AOM. A Cochrane review of randomised controlled trials (RCTs) of corticosteroids for AOM (two small studies; very low to low quality) indicated it might be useful clinically, but the small sample size and wide confidence intervals around the observed results leave too much uncertainty [20]. An additional RCT of corticosteroids showed a reduction of the duration of ear discharge in children with AOM and ventilation tubes [21]. Use of corticosteroids over a short duration is unlikely to cause harm. A systematic review identified side effects of short-course of corticosteroids (less than 2 weeks) in children, such as gastrointestinal disturbances and some behavioural changes. Due to diversity of corticosteroids' types and duration in included studies, the results were uncertain for both important beneficial and harmful effects of corticosteroids [22].

Accordingly, we plan to conduct an adequately powered clinical trial to address the uncertainties around the effectiveness of corticosteroids for AOM in children. Initially, we plan to conduct the pilot study described here with an associated mechanistic sub-study using tympanometry. The pilot study will test the feasibility of characteristics of our main study design and all the study procedures, as well as other operational strategies in our proposed main study. As one of our outcomes is to assess the ability to measure planned outcomes of the proposed main study, we will also obtain the outcomes and report these narratively. The mechanistic sub-study will explore the potential mechanism of action of corticosteroids in the resolution of middle ear effusion in AOM.

Methods/design

Study aims and objectives

As this is a pilot study, we aim to test all pre-specified methods and procedures that will be implemented in the main study, including the overall process, resources, management, and scientific components, in a smaller size study.

The objectives for the pilot study are (1) to assess the overall process and procedures of the main study (e.g. the recruitment, randomisation, outcome measurement), (2) to identify the experience and obstacles of physicians and patients during the study, and (3) to verify the sample size calculation for the main study. The objective for the mechanistic sub-study is to assess the mechanistic effect of corticosteroids in improving middle ear effusion in children with AOM using tympanometry.

Study design and setting

This is a pilot parallel, pragmatic, stratified, randomised, open-label, single-blind, controlled study in an allocation ratio of 1:1 (see Additional file 1. Protocol – Pilot OPAL Study).

We are going to conduct this study in seven hospitals in Jakarta and Bekasi: (1) Dr. Cipto Mangunkusumo Hospital, (2) Persahabatan Hospital, (3) Gatot Subroto Army Hospital, (4) Antam Medika Hospital, (5) Cempaka Putih Islamic Hospital, (6) Proklamasi ENT Hospital, and (7) Hermina Bekasi Hospital.

Participants

Inclusion criteria

We will include children aged 6 months to 12 years old with AOM, defined as current onset (within 48 h) of AOM-relevant symptoms (e.g. earache, ear tugging/rubbing or irritability in non-verbal children). Otoscopic findings of acute inflammation (e.g. erythema) and middle ear effusion (e.g. bulged tympanic membrane, immobile tympanic membrane, air fluid level) will confirm the

diagnosis. Due to the pragmatic nature of this study, we have chosen to reflect real practice, where physicians often solely diagnose AOM based on symptoms alone because of several limitations in visualising the ear drums (e.g. non-cooperative children, narrow ear canals, obstructing ear wax). Therefore, the otoscopic examination is not compulsory in diagnosing AOM. However, prior to the study, we will emphasise the importance of the use of otoscope in diagnosing AOM to the participating physicians and conduct training to visually identify clinical signs of AOM using otoscope.

Exclusion criteria

We will exclude children (1) with major and severe medical conditions (e.g. heart diseases, kidney failure, tuberculosis), (2) who are immunocompromised (e.g. HIV, in cancer treatment), (3) with congenital malformations and/or syndromes (e.g. cleft palate, Down's syndrome), (4) who have high risk of strongyloidiasis infections, (5) with ear ventilation tube(s), (6) who have been exposed to persons with varicella (chicken pox) or active Zoster infection in the past 3 weeks without prior varicella immunisation or infection, (7) who have taken systemic (oral, injection) or topical steroids in the preceding 4 weeks, (8) who have taken antibiotics in the preceding 2 weeks, and (9) who are hypersensitive to prednisolone or prednisone, or other corticosteroids.

Study intervention arm

Prednisolone tablets (Lupred®5) will be given at a dose of 1–2 mg/kg of body weight per day. As there is a wide therapeutic dose window for prednisolone, this will enable us to operationalise the dose as 10 mg/day for children aged 6 months to up to 2 years; 20 mg/day for children aged 2 up to 6 years; and 30 mg/day for children aged 6 to 12 years, simplifying both randomisation and dosage instructions. We determined the dose and duration of prednisolone based on the paediatric otitis media studies and other national and international practice guidelines of inflammatory and infectious diseases in children (e.g. bronchial asthma, juvenile rheumatoid arthritis, acute bacterial meningitis) [23–27]. An animal study [28] using mice infected with common causative bacteria of AOM (*Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*) demonstrated that most AOM-related cytokines (e.g. interleukin 1 alpha/IL-1α, tumour necrosis factor alpha/TNF-α) peaked at 3 to 6 h, progressively reduced on day 4 to day 6, and eventually were resolved after day 6. We will give the prednisolone for 5 days to boost the natural resolution process in middle ear inflammation and to minimise potential harms of corticosteroid use. A morning single daily dose (6 to 8 am) is preferable over divided doses to prevent the hypothalamic–pituitary–adrenal (HPA) axis suppression and for the convenience of the children and parents. Due to the bitter taste of prednisolone despite the addition of sweetener, we will advise the parents to mix the powder with jam or sweet juice to make it more palatable for the children.

We will stratify by disease severity and randomise children with mild AOM to receive prednisolone plus expectant observation, or expectant observation alone. Those with severe AOM will be randomly allocated to receive prednisolone plus antibiotic, or antibiotic alone.

Control arm

Budget constraints preclude us using matched placebo; children allocated to control group will not receive prednisolone but will receive standard care based on the severity of their AOM (i.e. observation for mild AOM, antibiotics for severe AOM).

Concurrent treatment

Prior to the randomisation, physicians may prescribe symptomatic medications (e.g. antipyretic, analgesic, decongestant) according to their usual practice. The physicians will not prescribe systemic corticosteroids. Therefore, the choice in prescribing these medications will not be influenced by subsequent knowledge of allocated treatment group.

Criteria for study drug discontinuation or modification

If children vomit less than 30 min after having a dose of prednisolone, parents should give the same dose again. However, if they vomit again after 30 min, parents should not give another dose of prednisolone until the next dose on the next day. If children keep vomiting after receiving prednisolone, parents should contact the research team. If the parents forget to give prednisolone to their children, they can give the missed dose as soon as they remember on the same day. To prevent this, we developed several reminder strategies, such as daily text-message reminders and a reminder note at the end of the first 5 days in a daily symptom dairy. This will remind the parents to give the study medication after completing the symptom diary on that particular day.

If there are any adverse events and adverse drug reactions which have been assessed by the research team that would require the discontinuation of drug study and further assessment and treatment, the treatment will be discontinued for this particular case; however, follow-up will continue, where possible.

Adherence monitoring

Participating physicians will provide information regarding the administration of the prednisolone with the prescription. One researcher will send daily text-message reminders to all of the parents in both prednisolone and control groups to (1) take the study medication regularly

(during the intervention period of 5 days), (2) complete the symptom diary daily until day 14 (2 weeks only), and (3) visit the clinic for re-assessment at day 3 (visit 1), day 7 (visit 2), day 30 (visit 3), and day 90 (visit 4). At visit 1 and visit 2, the parents will return the first and second mini booklets of symptom diary and the left-over drug to the appointed nurse (at visit 2) for assessment of adherence to study medication. We will visit the patients' homes at day 14 to collect the last (the third) mini booklet of symptom diary that will record the symptoms from day 7 to day 14 after the baseline visit (see Additional file 2. Case report forms – Pilot OPAL Study: CRF06. Symptom diary).

For participants and parents who are no longer willing to participate in the study (e.g. withdrawal from the study, not taking the study medication), we will still encourage them to come to their scheduled follow-up visit. This will enable us to collect the outcome data for those who are no longer in the study.

Outcomes

Our outcomes in this pilot study are to determine (1) the recruitment rates, (2) the success of the study procedures, (3) the ability to measure planned outcomes in the main study, (4) the compliance to study visits and study medication, and (5) the verification of sample size calculation for the main study.

Recruitment rate is defined as the proportion of consultations with potentially eligible children who provide their consent to be included in the study. This is a crucial aspect in a clinical trial. Low recruitment can result in a discontinuation of an on-going study [29]. We will assess this outcome at each month for the overall 6-month recruitment duration of the pilot study.

We will assess the success of the study procedures by identifying the process and obstacles during the following procedures: (1) obtaining informed consent from the patients and their parents; (2) recruitment using prespecified eligibility criteria and the use of otoscope to confirm AOM if feasible; (3) stratification and randomisation, including accessing the randomisation system and dispensing the study medication; and (4) identification of AOM symptoms and signs by clinical history taking and examination using otoscope and tympanometry. In AOM cases with earwax, we will extract the earwax before performing the otoscopy and tympanometry examination. If the earwax extraction is not feasible (e.g. uncooperative patients, cerumen prop), we will not include this patient in the mechanistic sub-study, but we still include this patient in the pilot study (as long as this patient fulfils the study criteria). Patients with tympanic membrane perforation will also not undergo tympanometry examination and will be included in the pilot study only. We will assess this outcome at the baseline visit (visit 0), day 3 (visit 1), day 7 (visit 2), day 30 (visit 3), and day 90 (visit 4).

We will identify the ability and challenges in measuring planned outcomes in the main study from the perspectives of participating physicians, nurses, and audiologists, as well as the eligible children and their parents. For example, we want to know whether it is difficult for the physicians to identify the pain severity using visual analogue scale (VAS) and acute otitis media severity of symptoms scale (AOM-SOS), as these are not common tools that are used in the management of AOM.

The compliance to study visits and study medication is defined as a proportion of children who regularly take the study medication according to the prespecified dose and duration (assessed using the symptom diary and the number of any left-over drug) and who come to follow-up visits per protocol. Participants will be followed closely by physicians and research staff. Children will return for a visit at day 3 after randomisation (visit 1), ensuring collection of the primary outcome.

The last outcome in this pilot study is to verify sample size calculation for the main study. Based on our size calculation, we must enrol 760 children with AOM. We estimated that there will be 35% of the total sample of children with AOM in the severe group (i.e. children with severe symptoms, fever ≥ 39 °C, children aged < 2 years with bilateral AOM, AOM with perforation of tympanic membrane). Within this pilot study, we will identify whether there will be a sufficient number of children for our main study in each stratum and the event rate in the control group.

We will also conduct a mechanistic sub-study using tympanometry. As a primary outcome, we will assess the change of middle ear effusion at similar time points with the pilot study. We will measure middle ear effusion using static acoustic admittance, defined as 'the amount of energy absorbed by the tympanic membrane and middle ear, measured in millimetre ohm or millilitre' [30]. The secondary outcomes are determining (1) the duration of middle ear effusion and (2) the correlation between ear pain and other symptoms (i.e. ear tugging, irritability, crying, lack of sleep, lack of appetite, loss of playfulness, fever) with the changes in middle ear effusion at various time points.

Assessing the feasibility of measuring planned outcomes in the main study (e.g. proportion of children with pain at day 3, proportion of children with pain and other non-specific AOM symptoms at various time points, adverse effects, recurrence) will provide the results for these outcomes. However, we will report these narratively due to a limited sample size and insufficient formal power calculation, which makes us unable to detect actual effects of corticosteroids to improve clinical outcomes in AOM.

Study procedure

Study site selection and training

In 2016, we tested feasibility of this study by surveying physicians (general practitioners; ear, nose, throat specialists; and paediatricians) in three cities (DKI Jakarta, Depok, Bekasi) in Indonesia, asking about current management of AOM in children, and their willingness to participate in our proposed main study. We found there were sufficient physicians who would prescribe corticosteroids for AOM among the 171 physicians from 87 primary/secondary to tertiary healthcare centres, in our proposed study. For practical reasons, we will only include seven hospitals in Jakarta and Bekasi.

To ensure that all procedures and the outcome data can be sufficiently conducted, collected, and recorded properly according to prespecified plans, we will conduct training for participating physicians prior to the implementation of the study. The training will include the implementation of a clinical trial based on good clinical practice guidelines, the summary of our study, and the procedural steps in our study from the eligibility identification, stratification, to data collection and management. We will also provide training for nurses, pharmacists, and tympanometry technicians in terms of the randomisation process, dispensing and preparing the study medication, and conducting and completing the outcome form for tympanometry examination (see Additional file 3. Manual of operations – Pilot OPAL Study and Additional file 4. Training slides – Pilot OPAL Study).

Recruitment and stratification

In the main study, we will stratify eligible children by the clinical specialty (primary care or secondary/tertiary healthcare centres) and severity of AOM (mild or severe). In this pilot study, we will only include ear, nose, throat (ENT) specialists who work in tertiary healthcare centres (see Fig. 1). Therefore, we will stratify the eligible children only based on their AOM severity. Children with mild AOM symptoms and signs (e.g. mild ear pain, fever < 39 °C) will be considered the mild AOM group, whilst those with moderate to severe symptoms and signs (e.g. moderate to severe ear pain, fever ≥ 39 °C, moderate to severe bulging of tympanic membrane, children aged < 2 years with bilateral AOM, AOM with perforated tympanic membrane, complications) will be considered the severe AOM group. We will then randomly allocate them to receive either single dose prednisolone for 5 days as an addition to expectant observation compared to observation alone (mild AOM group) or as an addition to antibiotics compared to antibiotic treatment alone (severe AOM group).

Randomisation and allocation concealment

All consenting children and their parents who are eligible will be enrolled and stratified based on their AOM severity by the participating physician. The eligibility and stratification which is provided by the physicians will help the appointed nurses to obtain the information from the randomisation website, developed by Centre for Research in Evidence-Based Practice (CREBP) Bond University, Queensland, Australia. The randomisation information for each subject is the intervention allocation and two-digit randomisation ID. A permuted block randomisation sequence will be computer-generated, prior to study commencement. The children will then be randomly allocated to either prednisolone and expectant observation or expectant observation alone in the mild group and either antibiotic with prednisolone or antibiotic alone in the severe group.

During the consultation, the physician will prescribe study medication for every study participant with the dose based on age, and the nurse will give the prescriptions to the participants who are allocated to the intervention group (prednisolone group). Using the prescription, the pharmacist will prepare the prednisolone by crushing the tablets based on the prescribed dose, mixing them with sweeteners, packing the mixed powder in daily paper medication packs for 5 days. This medication preparation procedure is commonly implemented for paediatric populations in Indonesia. The pharmacist will then dispense the study medication along with instructions for preparation and record the dispensing on the form provided by the study for this purpose. Batches of study medication will be dispatched to participating centres from a central pharmacy facility at the Clinical Research Supporting Unit, Faculty of Medicine Universitas Indonesia (CRSU FMUI).

Blinding

The appointed nurses, the study participants, and their parents will know the allocation of the intervention. We will ensure that the participating physicians and the audiologists/tympanometry technicians will be blinded to the intervention allocation until all study outcomes, particularly pain, at day 3 (visit 1) are collected. At day 3, study participants will meet the appointed nurses before having a consultation with the physicians or undergoing the tympanometry examination to ensure blinding of outcome assessors. Emergency unblinding, before day 3, can occur if there are serious adverse events (SAEs) and only limited to the particular physician and patient who is experiencing the SAE.

Follow-up timeline

We will measure the outcomes at various time points: (1) visit 1 after 48-h observation (day 3), (2) visit 2 (day 7), (3) visit 3 (day 30), and (4) visit 4 (day 90). In the main study, patients will visit the hospital at visit 1 and visit 2, whilst the last two visits will be home visits.

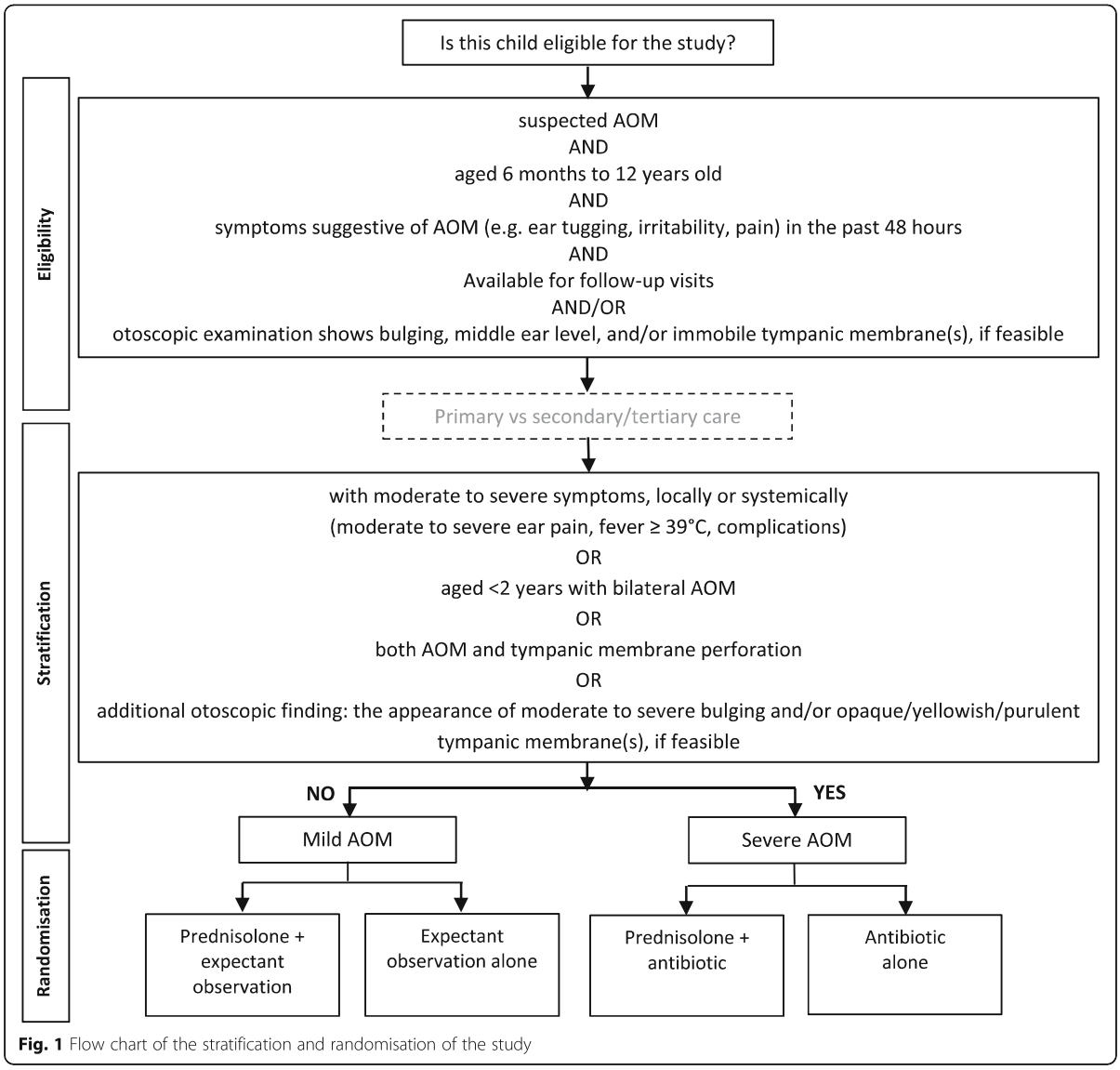


Fig. 1 Flow chart of the stratification and randomisation of the study

However, since the pilot study will be conducted simultaneously with the mechanistic sub-study, all the patients will have four hospital visits for tympanometry examination. We will do a home visit at the second week to collect the symptom diary (see Table 1).

Data collection

We will use a consent form, a recruitment log book, case report forms (CRFs), and a symptom diary to measure and record all outcomes. The case report forms consist of (1) eligibility form, (2) baseline information form, (3) outcomes form, (4) randomisation form, (5) study medication dispensing and return form, (6) feedback form, and (7) serious adverse effects form.

We will identify the recruitment rate by assessing the proportion of parents/children who provide their consent divided by the proportion of consultations with potentially eligible children during the study. We will use a study recruitment log book to record the reason(s) why children were not randomised.

We will assess the success of the study procedures using a feedback form. Using the feedback form, physicians, nurses, pharmacists, and the parents will rate their understanding and challenges they encountered during the implementation of study, including the completion of the case report forms and the symptom diary, the randomisation process, and dispensing and the preparing of study medication. They will grade the severity of the

Table 1 The schedule of enrolment, interventions, and assessments

	STUDY PERIOD					
	Enrolment Allocation	Post-allocation				Close-out
TIMEPOINT	0 (Day-0)	t1 (Day-3)	Intervention ends (Day-5)	t2 (Day-7)	t3 (Day-30)	t4 (Day-90)
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation	X					
INTERVENTIONS:						
[Intervention A] Prednisolone (5 days)	—	—	—			
[Intervention B] None (control) (5 days)	—	—	—			
ASSESSMENTS:						
Baseline examination (weight, height, BP, body temperature)	X	X		X	X	X
Severity of pain and duration using VAS	X	X		X		
Overall symptoms and its duration using AOM-SOS	X	X		X		
Adherence to study medication	X	X		X		
Adverse effects	X	X		X		
Otoscopic examination	X	X		X	X	X
Tympanometry examination	X[±]	X[±]		X	X	X
Complication	X	X		X		
Recurrence of acute otitis media					X	X

challenges or obstacles on a scale with a range from very easy to very difficult (see Additional file 2. Case report forms—Pilot OPAL Study: CRF11. Feedback form).

To assess the ability to measure planned outcomes in the main study, we will also use a feedback form to identify the understanding, the challenges, and the complexity of the outcome assessment tools utilised for this study (i.e. CRFs and patient symptom diary) from the perspective of the study participants, their parents, and the participating physicians (see Additional file 2. Case report forms—Pilot OPAL Study: CRF05. Outcome form and CRF06. Symptom diary). The CRFs and symptom diary will record the clinical history and symptoms (e.g. VAS, AOM-SOS), as well as physical examination (e.g. temperature, blood pressure, otoscopic examination if feasible). The VAS is acknowledged as a well-established and validated scale for assessing pain [31]. It has a 100-mm horizontal scale with 'no pain' anchor at the left and 'the most severe pain' at the right endpoint of the scale. The scale will be determined by measuring the distance from the left endpoint ('no pain') to the line representing the pain level, marked by the parents or older study participants (≥ 8 years old) [32]. A 10-mm difference has been reported to indicate a clinically significant change [33, 34]. The AOM–SOS is used to assess the severity of other acute otitis media-relevant symptoms daily and activity limitation due to acute otitis media in the proceeding 12 to 24 h [35], particularly in non-verbal children, using a scale of 'no,' 'a little,' and 'a lot'. Shaikh et al. [35] used the mean of 4.2 points as a minimal

important difference. We have translated the original (English) version of AOM–SOS to an Indonesian version of AOM–SOS through forward and backward translation process.

The compliance to the study and study medication will be measured by assessing the completion of CRFs and symptom diary, particularly the attendance of the study participants and their parents to their scheduled follow-up visits, the completion of the study medication based on the symptom diary, and the left-over drug.

We will use the CRFs to assess the verification of sample size calculation for the main study.

Data management

The integrity and completion of data will be maintained through consistency checks during data entry and cross-checks between items after data entry. All the actions and modifications to data stored in the database will be documented and retrievable for viewing. Any modification to original forms will be documented with the date, name, and signature on paper and electronic versions. Missing data or errors will be detected before final submission to the electronic central database. This central database will be checked regularly for its validity and completeness of study data and will be protected with a regular complete backup system.

Sample size

Even though our sample size calculation for our proposed main study demonstrated that we need to recruit 760 children with AOM, we did not formally determine the sample size for this pilot study. There are several suggestions in calculating the sample size for a pilot study (e.g. at least 55 participants or at least 9% of the sample size of the main study) [36]. Since we will need 60 children for our mechanistic sub-study, we will also include 60 children with AOM in our pilot study. The sample size of the mechanistic sub-study was determined based on the main primary outcome, which is the mean value of static acoustic admittance or acoustic compliance in the tympanometry findings. In a previous study of children with middle ear effusion who underwent tympanometry assessment and had a history of chronic or recurrent middle ear disease [37], the response within each subject group was normally distributed with standard deviation 0.3. If the true difference in the experimental and control means is 0.3 units, we will need to study 22 experimental subjects and 22 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The type I error probability associated with this test of this null hypothesis is 0.05. With a 20% allowance for dropouts, the total sample size becomes 56; consequently, we will include 60 children for this pilot study.

We will recruit children with AOM from seven tertiary healthcare centres that have tympanometry and are located in eastern and central Jakarta. Our survey study demonstrated that there were sufficient numbers of potential paediatric AOM patients (97 children with AOM in a week) and physicians (50 physicians) who were willing to participate in the study at these hospitals, meaning physicians see between 1 and 2 potentially eligible patients/week. Using a worst-case scenario, we assumed that only 30% of physicians would participate and only 25% of patients would give consent to participate in our study, equating to a maximum of 29 children per month. However, it is likely to take several weeks to months for sites to recruit to optimum levels, so we have allowed 6 months to recruit 60 children with AOM. The study duration will be 9 months: 6 months for recruitment plus 3 months for final follow-up data collection (3 months post-enrolment).

In order to achieve adequate participant enrolment, we will train nurses in each hospital on how to screen all children with acute ear symptoms (e.g. ear pain, ear tugging, ear discharge). We will ensure all study documents are accessible by providing binders of study recruitment log book and case report forms at nursing stations. In the first 2 weeks of the study (at least 3 days per week), a researcher will also stand-by at the hospital to help the nurses to identify and screen children with suspected AOM.

Statistical methods

For the recruitment rate, we report the outcome as the proportion of children in percentages. For the success of the study procedures and the ability to measure planned outcomes in the main study, we will report the outcomes as the proportion of physicians in percentages based on the grading scale of their feedback report on prespecified outcome measure tools. For the compliance to study visits and study medication, we will report the outcomes as the proportion of children in percentages who attend the follow-up visits and complete the cycle of study medication.

To assess the verification of sample size calculation for main study, we will report this outcome as the proportion of children in each stratum (mild and severe acute otitis media group) and those with pain at day 3 after randomisation in the control group.

Although we will not formally report the clinical outcomes due to a limited sample size and insufficient formal power calculation of this pilot study, we will report and analyse the clinical outcomes of the mechanistic sub-study using tympanometry. We plan to analyse by intention-to-treat; however, if there is loss to follow-up,

we will not impute data, but use an available case analysis, due to the small sample size. We will still record data on those who stop study medication, where possible, and will include them in the analysis. For the mechanistic sub-study, we will report continuous variables (i.e. the change in middle ear effusion at various time points (mean in day; standard deviation), the duration of middle ear effusion, the difference between two groups) as a mean difference with 95% confidence intervals (CI). We will also report the correlation between ear pain and other symptoms with the changes in middle ear effusion at various time points.

Data monitoring

Since this is a short study, this pilot study does not require a data monitoring committee. However, independent personnel from Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit, Dr. Cipto Mangunkusumo Hospital (CMH) – Faculty of Medicine Universitas Indonesia (FMUI), who are not involved in this study, will assess the process and the quality of patient recruitment, data entry, and a compilation of research data in the central database. Serious adverse event cases will be identified, assessed, and managed by physicians. These cases will then be recorded and reported to, as well as be reviewed by the Medical Ethics Committee Faculty of Medicine Universitas Indonesia (FMUI) (Indonesia) and the Bond University's Human Research Ethics Committee (BUHREC) (Australia).

Interim analysis

Due to the small number of recruited patients to the study and because the duration of the study will be less than 1 year, we will not conduct an interim analysis.

Harms

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with study medication, whereas adverse effects or adverse drug reactions are defined as all noxious and unintended responses to a study medication related to any dose. Adverse events and adverse drug reaction will be collected after parents of the eligible children sign the written consent and being enrolled in the study. All adverse events occurring after the enrolment into the study, during the additional treatment, or hospitalisation due to adverse events and/or adverse drug reaction will be recorded. A subject who experiences serious adverse events, defined as any untoward medical occurrence at any dose that may result in-patient and/or prolonged hospitalisation, persistent or significant disability, medically important events, life-threatening events, and death, will receive sufficient treatment and will be recorded and reported to the Medical Ethics Committee FMUI and the BUHREC. We will not report serious adverse events occurring after the study discontinuation, unless there is a temporal relationship between study medications or other protocol procedure to the events, as well as whether the event is unexpected or unexplained given the subject's clinical course, previous medical conditions, and concomitant medications. All the serious adverse events will be recorded in the serious adverse event form.

Auditing

For the main study, we will establish an audit committee from the CRSU FMUI and CEEBM Unit CMH-FMUI which is independent from the study investigators. Observation and quality assessment of the study will be ensured to be always in accordance with the protocol and International Conference Harmonization – Good Clinical Practice (ICH-GCP) standards. However, we will not conduct this in the pilot study because it is a short and small size study.

Protocol amendments

Any modifications to the protocol which may impact on the study process (e.g. modification of study objectives, study design, study population, sample sizes, study procedures), potential benefits, and safety of the patients will require a formal amendment to the protocol. This amendment will be notified and approved by the Ethics committee prior to its implementation. Notification will also be sent to the health authorities in accordance with local regulations. Minor modifications that may not impact on the study process will only be notified to the Ethics committee.

Confidentiality

All information related to the study will be securely stored using password-protected access systems. These forms will be kept confidential by only using coded patient IDs as identifiers and will be stored separately from all forms and records that contain names or other identifiers (e.g. informed consent forms). All counselling sessions, including general, ear-nose-throat, and tympanometry examinations, will be conducted in private rooms. All the involved research staff such as physicians, nurses, audiologists, and pharmacists will be required to sign agreements to preserve the confidentiality of all participants. The confidentiality of every participant will be maintained and will not be distributed externally without the written permission of the participant, except for medical and research safety purposes by national regulatory authorities if necessary.

Access to data

The principal investigator will be given access to the cleaned data sets. She will also have direct access to each site's data sets and by request. Project data sets will be secured using passwords. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Ancillary and post-study care

Short-term corticosteroids are very unlikely to have harm outside those we will be measuring. However, we will observe any potential adverse effects from the study medication using a symptom diary. The symptom diary will record adverse effects commonly found in corticosteroid treatment (e.g. gastrointestinal disturbance, behavioural changes), AOM complications (e.g. eardrums perforation, mastoiditis), and also the severity of pain and other non-specific symptoms of AOM. We will provide a 24-h call centre for any emergency assistance and send regular text reminders to the parents (for taking medication and completing the diary), where parents will be able to report any deteriorating or worsening symptoms of AOM. We will also provide a list of healthcare providers to manage emergency cases that might occur during the study. We will be responsible for the adverse effects that will occur from the study medication during and after the study related to study medication. The compensation will include the treatment cost relevant with the study medication, such as consultation visits, additional examinations, and treatment (e.g. medicine, hospitalisation cost). Due to other potential concurrent treatments within the study medication, there will be robust review and analysis process to conclude the cause of adverse events. Information of management of adverse effects will be provided by physicians during the process of consent approval before entering the study. We will also include this information in the patient symptom diary, including the 24-h emergency call and list of recommended healthcare providers.

Dissemination policy

Study results, either statistically significant or non-significant, will be reported in a journal manuscript after being distributed to all the investigators to be reviewed.

The authorships and contributions of this study will be acknowledged on the protocol, manuscript, and the report. Before the publication in medical journal or paper presentation, the principal investigators will provide written consent of their acknowledgment and contribution in the reported study.

Reproducible research

We will make the full protocol of this study to be publicly available to maintain its transparency and reproducibility. This full protocol will include detailed information regarding the study, particularly on study design and conduct that not are commonly included in the published protocol or information description in clinical trial registry. We have registered the protocol at the Australian and New Zealand clinical trial registry (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12618000049279). We will also publish the results of this study in relevant medical journals as two separate papers as the following: (1) results of the pilot study and (2) results of the mechanistic sub-study. If necessary, we will include the anonymised participant-level dataset in its appendix or online. Unpublished outcomes will be reported in the full study report that will be linked to the published study.

Discussion

By conducting this pilot study and mimicking all the procedures in the main study, it enables us to identify any practical or operational issues in performing the main study (e.g. the recruitment and stratification process, outcome measurement, randomisation process, the compliance to the study). Our mechanistic sub-study will demonstrate whether the potential mechanism of action of corticosteroid will improve the resolution of middle ear effusion in AOM cases and whether the changes correlate with clinical symptoms of AOM.

We also presume that there are will be several challenges during the implementation of the main study, particularly in these following processes: (1) data collection using otoscopes, as is not compulsory due to the pragmatic design and the potential difficulties to visualise the children's tympanic membranes; (2) the stratification and the management of AOM according to the AOM severity, particularly for children in the mild AOM group, due to unclear classification of AOM severity and antibiotic treatment for AOM in Indonesia; (3) clinical outcome measurement using the AOM symptom reporting tools (e.g. VAS, AOM-SOS, symptom diary) as this is still not practiced in the management of AOM; and (4) the randomisation process using a randomisation centre website to simplify the randomisation allocation process. This will be a new and challenging experience for most of the participating nurses who will run the randomisation.

We have identified several limitations in our study. The first limitation is we will only include seven hospitals in Jakarta and Bekasi, which will not represent the coverage of the main study that will involve more than 50 primary/secondary and tertiary healthcare centres. The second one is limited reliability of outcome assessment instruments due to wide range of ages in this study. The VAS has a limited reliability in self-report in young children due to their lack of cognitive skills and experience with scaling and estimating the magnitude. The parents will assess the severity of the pain on

children aged up to 8 years old [34], whilst the AOM–SOS will also be used to assess the symptoms and activity limitation due to acute otitis media, which might be better in younger children (< 2 years).

This pilot study is crucial to ensure the successful implementation of the main study. The main study will provide high-quality evidence about the value of corticosteroid in improving the resolution of AOM (e.g. pain and other symptoms, middle ear effusion, recurrence). If positive, it will provide an alternative to antibiotics for children with mild symptoms, and a useful addition to antibiotics in those with severe disease. If negative, it will provide opportunity for researchers to test other potential alternatives for improving the clinical outcomes of AOM.

By conducting this study, we will determine the importance of (1) the identification of AOM severity in determining a sufficient, comprehensive, and evidence-based management of AOM and (2) the use of symptom assessment tools in the management AOM by introducing several feasible validated tools. This can improve the quality of the management of AOM, particularly in reducing the use of antibiotics for mild AOM. As part of capacity building support for health practitioners (i.e. physicians, nurses, audiologists, pharmacists) in Indonesia, this study will provide opportunity for them to be directly involved in clinical research and to develop their capacity for future research.

Study status

We began recruitment on 22 February 2018. The protocol as described here was finalised on 17 October 2017.

Additional files

Additional file 1: Protocol—Pilot OPAL Study. This file is a protocol of a pilot pragmatic, randomised, open-label, controlled study of an oral prednisolone for acute otitis media in children. This file can be accessed at https://pure.bond.edu.au/ws/portalfiles/portal/27513682/Additional_File_1._Protocol_Pilot_OPAL_Study.pdf (PDF 491 kb)

Additional file 2: Case report forms—Pilot OPAL Study. This file includes case report forms that are used in the pilot study: CRF01. Participant information sheet and consent form; CRF02. Study registration form; CRF03. Eligibility form; CRF04. Baseline information form; CRF05. Outcome form; CRF06. Symptom diary; CRF07. Prescription of study medication; CRF08. Randomisation form; CRF09. Follow-up visit card; CRF10. Serious adverse events reporting form; CRF11. Feedback form; FORM01. Study recruitment log book; FORM02. Study medication stock book; FORM03. Study medication dispensing form; FORM04. Study medication return form; FORM05. Completed case report form; FORM06. Recapitulation of non-participating subject form; FORM07. Guideline of antibiotics for acute otitis media; FORM08. Prednisolone dose for OPAL study; FORM09. Instruction for using prednisolone for parents; FORM10. Lupred pharmaceutical brochure. This file can be accessed at https://pure.bond.edu.au/ws/portalfiles/portal/27513684/Additional_File_2._Case_report_forms_Pilot_OPAL_Study.pdf (PDF 4716 kb)

Additional file 3: Manual of operations—Pilot OPAL Study. This file includes step-by-step manual for physicians, audiologists, nurses, and pharmacists who participate in the study. The manual of operations handbook was distributed during the trainings for participating physicians, audiologists, nurses, and pharmacists. This file can be accessed at https://pure.bond.edu.au/ws/portalfiles/portal/27513686/Additional_File_3._Manual_of_Operations_Pilot_OPAL_Study.pdf (PDF 7905 kb)

Additional file 4: Training slides—Pilot OPAL Study. The training slide was presented during the training for participating physicians, audiologists, nurses, and pharmacists. The training was conducted prior to the study commencement. This file can be accessed at https://pure.bond.edu.au/ws/portalfiles/portal/27513688/Additional_File_4._Training_Slides_Pilot_OPAL_Study.pdf (PDF 5528 kb)

Abbreviations

ADR: Adverse drug reaction; AOM: Acute otitis media; AOM-SOS: Acute otitis media severity of symptoms scale; BUHREC: Bond University's Human Research Ethics Committee; CEEBM CMH – FMUI: Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo General Hospital – Faculty of Medicine Universitas Indonesia; CRF: Case report form; CRSU FMUI: Clinical Research Supporting Unit, Faculty of Medicine Universitas Indonesia; ICH-GCP: International Conference Harmonization – Good Clinical Practice; ID: Identifier; IL-1α: Interleukin-1 alpha; IL-6: Interleukin-6; NTHi: Non-typeable *Haemophilus influenzae*; ORL: Otorhinolaryngologist; RCT: Randomised controlled trial; SAE: Serious adverse event; TNF-α: Tumour necrosis factor alpha; VAS: Visual analogue scale

Acknowledgments

We thank Professor Sudigdo Sastroasmoro, MD, PhD, Paediatrician and Arie Sulistyowati, MD, MSc, Paediatrician for their support and feedback in the development of the protocol and the implementation of the study. We also thank Professor Paul Glasziou, FRACGP, PhD as a Director of Centre for Research in Evidence-Based Practice, Bond University, Queensland, Australia, and Professor Siti Setiati, MD, PhD, Geriatrician, M.Epid as a Director of Clinical Epidemiology and Evidence-Based Medicine Unit Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia for their support in the preparation and implementation of this study; the Directors and the Head of Departments of Otorhinolaryngology – Head and Neck Surgery of Dr. Cipto Mangunkusumo Hospital (CMH), Persahabatan General Hospital (PGH), Gatot Subroto Army Hospital (GSAH), Proklamasi Ear, Nose, and Throat Centre (Proklamasi), Antam Medika Hospital (AMH), and Islamic Hospital Cempaka Putih (IHCP); Yulvina, MD, ORL; Evita F. Edyani, MD, ORL; Hably Warganegara, MD, ORL, for supporting and coordinating the recruitment of study participants in each study site; and Neil Roberts and Cameron Lydster, Bond University, for the assistance with proofreading.

Funding

This research is supported by an Australian Government Research Training Program Scholarship and funded by the Australian National Health and Medical Research Council (NHMRC) [#1044904] as part of the Centre for Research Excellence in Minimising Antibiotic Resistance for Acute Respiratory Infections (CREMARA) and the Advance Queensland, Australia [Women's Academic Fund Maternity funding WAF-7026811-298]. These funding bodies had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Availability of data and materials

Our manuscript does not contain any data as it is a study protocol. However, we will provide additional files, such as the protocol, case report form, manual of operations, and training slides (https://research.bond.edu.au/en/publications/oral-prednisolone-for-acute-otitis-media-in-children-opal-study-a). We will also provide the datasets used and/or analysed of the pilot study when are available. This can be accessed by a reasonable request to the corresponding author.

Authors' contributions

RWR, AMC, EMB, and CDM contributed in the study design and study protocol development. EDS and YP contributed in the study protocol development (the mechanistic sub-study section). WN contributed in the development of research permit and recruitment strategy. All authors have read and approved the final manuscript.

Ethics approval and consent to participate
This study protocol was reviewed and approved by the Ethics Committee FMUI Indonesia (No. 852/UN2.F1/ETIK/2017 and Amendment No. 1088/UN2.F1/ETIK/X/2017) and the BUHREC Australia (No. 16151 and Amendment No. 16208). We received approval for conducting clinical research from the One Stop Integrated Service Agency Province of DKI Jakarta (No. 0204/AF.1/31/-1.862.9/2017). We will also seek clinical study permits from the Training and Research division at each participating hospital.
We will provide the patient information sheet, including the whole study process and procedures and potential risks from the study, and obtain consent from the parent(s) or legal guardian of patients, before conducting the recruitment and randomisation process. However, for children aged 12 years, they have also to provide their consent to participate in the study (Additional file 2. Case report forms—Pilot OPAL Study: CRF01. Information sheet and consent form). The person who delivers the consent also will provide their signatures on the consent form, stating that they have provided information and opportunity for potential participants to understand and raise relevant questions to the study. We will ensure that the consent process is free of coercion. As the participation into the study is voluntary, we will emphasise their rights to withdraw from the study at any time without any consequences, particularly on the quality of their healthcare services.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Received: 26 March 2018 Accepted: 29 August 2018
Published online: 10 September 2018

References
1. World Health Organization: Global action plan on antimicrobial resistance. World Health Organization. 2015; http://www.who.int/iris/handle/10665/193736.
2. Harris AM, Hicks LA, Qaseem A. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Clinicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164:425–34.
3. Pettigrew MM, Gent JF, Pyles RB, Miller AL, Nokso-Koivisto J, Chonmaitree. Viral-bacterial interactions and risk of acute otitis media complicating upper respiratory tract infection. J Clin Microbiol 2011;49(11):3750–3755.
4. Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, et al. Viral upper respiratory tract infection and otitis media complication in young children. Clin Infect Dis. 2008;46(6):815–23.
5. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. Clinical practice guideline: the diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964–e99.
6. Liese JG, Silfverdal SA, Giaquinto C, Carmona A, Larcombe JH, Garcia-Sicilia J, et al. Incidence and clinical presentation of acute otitis media in children aged <6 years in European medical practices. Epidemiol Infect. 2014;142:1778–88.
7. Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. Pediatrics. 2017;140(3):e20170181.
8. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368:1429–35.
9. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096. https://doi.org/10.1136/bmj.c2096.
10. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2015;6:CD000219. https://doi.org/10.1002/14651858.CD000219.pub4.
11. McCullough AR, Pollack AJ, Hansen MP, Glasziou PP, Looke DFM, Britt HC, et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. Med J Aust. 2017;207(2):65–9.
12. Ministry of Health Republic of Indonesia. Clinical practice guidelines for clinicians in primary healthcare centres. Jakarta: Ministry of Health Republic of Indonesia; 2014. Regulatory No. 5 year 2014
13. Otology Working Group of Indonesian Otorhinolaryngologist Head and Neck Surgeon Society. Guidelines of ear, nose, and throat diseases in Indonesia [Guideline penyakit THT di Indonesia]. Jakarta: Indonesian Otorhinolaryngologist Head and Neck Surgeon Society; 2007.
14. Marom T, Marchisio P, Tamir SO, Torretta S, Gavriel H, Esposito S. Complementary and alternative medicine treatment options for otitis media. Medicine. 2016;95(6):e2695.
15. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database Syst Rev. 2008;3:CD001727. https://doi.org/10.1002/14651858.CD001727.pub4.
16. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, et al. A randomised, placebo-controlled trial of the effect of antihistamine of corticosteroid treatment in acute otitis media. J Pediatr. 2003;143:377–85.
17. Juhn SK, Jung MK, Hoffman MD, Drew BR, Preciado DA, Sausen NJ, et al. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. Clin Exp Otorhinolaryngol. 2008;1:117–38.
18. Chen Y, Li K, Pu H, Wu T. Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2011;3:CD007720. https://doi.org/10.1002/14651858.CD007720.pub2.
19. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015;9:CD004405. https://doi.org/10.1002/14651858.CD004405.pub5.
20. Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. Cochrane Database Syst Rev. 2018;3:CD012289. https://doi.org/10.1002/14651858.CD012289.pub2.
21. Ruohola A, Heikkinen T, Jero J, Puhakka T, Juvén T, Närkiö-Mäkelä M, et al. Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes. J Pediatr. 1999;134:459–63.
22. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child 2016;0:1–6. Doi: https://doi.org/10.1136/archdischild-2015-309522.
23. Indonesian Pediatric Society. Juvenile rheumatoid arthritis. In: Pudjiadi AH, Hegar B, Handryastuti S, et al., editors. Clinical guideline Indonesian Pediatric Society. 2nd ed. Jakarta: Indonesian Pediatric Society Publishing; 2011. p. 1–4.
24. Indonesian Pediatric Society. Acute bronchial asthma. In: Pudjiadi AH, Hegar B, Handryastuti S, et al., editors. Clinical guideline Indonesian Pediatric Society. Jakarta: Indonesian Pediatric Society Publishing; 2009. p. 269–73.
25. Indonesian Pediatric Society. Bacterial meningitis. In: Pudjiadi AH, Hegar B, Handryastuti S, et al., editors. Clinical guideline Indonesian Pediatric Society. Jakarta: Indonesian Pediatric Society Publishing; 2009. p. 189–92.
26. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. British Thoracic Society/Scottish Intercollegiate Guidelines Network. Revised edition; 2016. p. 107.
27. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2016. https://ginasthma.org/. Updated 2016. Accessed 2 Sept 2016.
28. Melhus A, Ryan AF. Expression of cytokine genes during pneumococcal and nontypeable Haemophilus influenzae acute otitis media in rat. Infect Immun. 2000;68(7):4024–31.
29. Denhoff ER, Milliren CE, de Ferranti SD, Steltz SK, Osganian SK. Factors associated with clinical research recruitment in a pediatric academic medical center—a web-based survey. PLoS One. 2015;10(10):e0140768. https://doi.org/10.1371/journal. pone.0140768.
30. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: otitis media with effusion (update). Otolaryngol Head Neck Surg. 2016;154(1S):S1–41.
31. Huguet A, Stinson JN, McGrath PJ. Measurement of self-reported pain intensity in children and adolescents. J Psychosom Res. 2010;68:329–36.
32. Cohen LL, Lemanek K, Blount RL, et al. Evidence-based assessment of paediatric pain. J Pediatr Psychol. 2008;33(9):939–56.
33. Von Baeyer C. Children's self-report of pain intensity: what we know, where we are headed. Pain Res Manag. 2009;14(1):39–45.
34. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analogue pain score for children. Ann Emerg Med. 2001;37(1):28–31.

35. Shaikh N, Hoberman A, Paradise JL, et al. Responsiveness and construct validity of a symptom scale for acute otitis media. Pediatr Infect Dis J. 2009; 28(1):9–12.
36. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. J Clin Epidemiol. 2013;66:197–201.
37. Nozza RJ, Bluestone CD, Kardatzke D, Bachman R. Identification of middle ear effusion by aural acoustic admittance and otoscopy. Ear Hear. 1994;15:310–23.

Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, controlled study (OPAL study)

1. Respati W. Ranakusuma, MD, ORL (Corresponding author)
   - Institute for Evidence-Based Healthcare
     Faculty of Health Sciences and Medicine Bond University
     14 University Drive, Robina 4226, Queensland, Australia
   - Clinical Epidemiology and Evidence-Based Medicine Unit
     Dr. Cipto Mangunkusumo General Hospital – Faculty of Medicine Universitas Indonesia
     Diponegoro 71, Jakarta 10430, Indonesia
   Email address: respati.ranakusuma@ceebm.org
2. Dr. Amanda R. McCullough, PhD, PGCHET, BSc (Hons)
   Faculty of Health Sciences and Medicine Bond University
   14 University Drive, Robina 4226, Queensland, Australia
   Email address: amccullo@bond.edu.au
3. Eka Dian Safitri, MD, ORL
   Clinical Epidemiology and Evidence-Based Medicine Unit
   Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
   Diponegoro 71, Jakarta 10430, Indonesia
   Email address: ekadian.safitri@ceebm.org
4. Yupitri Pitoyo, MD, ORL
   Clinical Epidemiology and Evidence-Based Medicine Unit
   Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
   Diponegoro 71, Jakarta 10430, Indonesia
   Email address: yupitri.pitoyo@ceebm.org
5. Widyaningsih, MPH
   Clinical Epidemiology and Evidence-Based Medicine Unit
   Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
   Diponegoro 71, Jakarta 10430, Indonesia
   Email address: widyaningsih.ade@ceebm.org
6. Professor Christopher B Del Mar, FAFPHM, MA, MD, FRACGP, BSc
   Institute for Evidence-Based Healthcare
   Faculty of Health Sciences and Medicine Bond University

14 University Drive, Robina 4226 Queensland, Australia
Email address: cdelmar@bond.edu.au

7. Associate Professor Elaine M. Beller, BSc, MAppStat
Institute for Evidence-Based Healthcare
Faculty of Health Sciences and Medicine Bond University
14 University Drive, Robina 4226 Queensland, Australia
Email address: ebeller@bond.edu.au

Abstract

Background: Acute otitis media (AOM) is associated with high antibiotic prescribing rates. Antibiotics are somewhat effective in improving pain and middle ear effusion (MEE) however they have unfavourable effects. Alternative treatments, such as corticosteroids as anti-inflammatory agents, are needed. Evidence for the efficacy of these remains inconclusive. We conducted a pilot study to test feasibility of a proposed large-scale randomised controlled trial (RCT) to assess the efficacy of corticosteroids for AOM.

Methods: We conducted a pilot, pragmatic, parallel, open-label RCT of oral corticosteroids for paediatric AOM in primary and secondary/tertiary care centres in Indonesia. Children aged 6 months-12 years with AOM were randomised to either prednisolone or control (1:1). Physicians were blinded to allocation. Our objectives were to test the feasibility of our full RCT procedures and design, and assess the mechanistic effect of corticosteroids, using tympanometry, in suppressing middle ear inflammation by reducing MEE.

Results: We screened 512 children; 62 (38%) of 161 eligible children were randomised and 60 were analysed for the primary clinical outcome. All study procedures were completed successfully by healthcare personnel and parents/caregivers, despite time constraints and high workload. All eligible, consenting children were appropriately randomised. One child did not take the medication and four received additional oral corticosteroids. Our revised sample size calculation verified 444 children are needed for the full RCT. Oral corticosteroids did not have any discernible effects on MEE resolution and duration. There was no correlation between pain or other symptoms and MEE change. However, prednisolone may reduce pain intensity at Day 3 (Visual Analogue Scale mean difference -7.4 mm, 95% confidence interval (CI) -13.4 to -1.3, p=0.018), but cause drowsiness (relative risk (RR) 1.8, 95% CI 1.1 to 2.8, p=0.016). Tympanometry curves at Day 7 may be improved (RR 1.8, 95% CI 1.0 to 2.9). We cannot yet confirm these as effects of corticosteroids due to insufficient sample size in this pilot study.

Conclusions: It is feasible to conduct a large, pragmatic RCT of corticosteroids for paediatric AOM in Indonesia. Although oral corticosteroids may reduce pain and improve tympanometry curves, it requires an adequately powered clinical trial to confirm this.

Keywords: Otitis media, Acute disease, Anti-bacterial agents, Glucocorticoids, Corticosteroids, Middle ear effusion, Pilot projects, Acoustic impedance tests.

Trial registration: Study registry number: ACTRN12618000049279. Name of registry: the Australian New Zealand Clinical Trials Registry (ANZCTR). Date of registration: 16 January 2018.

Background

Antibiotic resistance is a global health threat, largely because of antibiotic use [1-3]. Use of antibiotics is also associated with unfavourable effects (e.g. vomiting, diarrhoea) [4]. There is a particularly high rate of antibiotic prescribing for acute respiratory infections (ARIs) in outpatient settings (primary and secondary care): 50% in the United States; 53% in European countries; 34% in Malaysia; and up to 78% in Indonesia [5-8].

Acute otitis media (AOM), a middle ear inflammation, is an ARI that is commonly found in children, particularly before the age of five [9-10]. Antibiotics are commonly prescribed. A Cochrane review showed antibiotics are effective in improving acute pain and tympanometry results, as well as other clinical outcomes (e.g. tympanic membrane perforation, contralateral AOM). However, due to their modest benefits along with significant potential for unfavourable effects, antibiotics are not mandatory treatment for AOM, particularly for mild AOM. Therefore, it is important to emphasize both benefits and harm of antibiotic use to the patients and their parents and involve them in treatment decision making in the management of AOM.

In Australia, 89% of new AOM cases were managed by antibiotics between 2010 and 2015 [11]. In Indonesia, our feasibility survey showed that up to 88% of physicians would prescribe antibiotics for mild AOM, although antibiotics are most beneficial for severe AOM (i.e. severe symptoms, young children with bilateral AOM, tympanic membrane perforation) [9]. These rates are higher compared to other western countries such as the United States (57.6%), Iceland (70.4%), Denmark (73.7%), and Sweden (86.7%) [12-14]. This condition may be affected by two contradictory Indonesian practice guidelines for AOM [15,16]. The AOM guideline for primary care practitioners recommends the use of antibiotics for both mild and severe AOM. The only difference is the antibiotic dose, which recommends a higher dose for severe AOM [15]. On the other hand, the guideline for Ear, Nose, and Throat (ENT) specialists recommends antibiotic use for only severe AOM, although it does not specifically describe the definition of severe AOM [16]. In addition, despite of the existence of national regulation on antibiotic use, its implementation is less enforced in Indonesia and leads to antibiotic self-medication [17,18].

High rates of antibiotic use, despite of its modest benefits and side effects and antibiotic resistance, indicate the necessity to find effective alternative treatments for AOM (e.g. decongestants, herbal preparations, corticosteroids) [19-21]. The existing alternative treatments

have insufficient evidence to be recommended in clinical practice [19-21]. Since inflammation is a key mechanism of AOM, corticosteroids are a potential treatment. Although they have been effectively used for other ARIs (e.g. pneumonia, bacterial meningitis) [22,23], their effect on AOM remains unclear [24,25]. Aside from potential beneficial effects on inflammation, corticosteroids also may cause side effects. Gastrointestinal disturbances and behavioural changes have been identified as common side effects [26]. Although short-term use of a corticosteroid is unlikely to induce serious harm, one systematic review reported 1% of children experienced increased susceptibility to infections due to the immunosuppression effect of corticosteroids [26].

Our Cochrane review shows that systemic corticosteroids may effective in improving clinical symptoms of AOM [24]. However, this was based on one small study demonstrating uncertain effects of systemic corticosteroids for AOM due to a wide confidence interval that included both benefits and harm. High-quality evidence is crucial to address uncertainties around the effects of corticosteroids for AOM. Therefore, we plan to conduct an adequately powered clinical trial to assess both benefits and harm of corticosteroids for children with AOM. Our original sample size calculation demonstrated that we need 760 children to be able to detect actual effects of oral corticosteroids for children with AOM. Prior to this, we conducted a pilot study to test the feasibility of characteristics of our full RCT design and procedures in 60 children, including a mechanistic sub-study using tympanometry (tympanometry sub-study) to study the effect of corticosteroids on middle ear effusion (MEE). The clinical findings from this study, although they cannot be definitive due to a small sample size, can indicate the direction of potential clinical effects of oral corticosteroids for AOM, which can then be confirmed in an adequately powered clinical trial.

Methods

Study aims and objectives

This pilot study aimed to test all pre-specified methods and procedures that are planned to be implemented in the full RCT, but in a smaller sized study.

The objectives for the pilot study were to assess the feasibility of characteristics of the full RCT design and procedures (e.g. recruitment, randomisation, outcome measurement, experience and obstacles of physicians and parents/caregivers, sample size verification) and

assess the mechanistic effect of corticosteroids in suppressing inflammation in the middle ear specifically by reducing MEE.

Prior to our study implementation, our study protocol was reviewed and approved by the Ethics Committee Faculty of Medicine Universitas Indonesia and the Bond University Human Research Ethics Committee (BUHREC) Australia (see Declarations section).

Study design and setting

This was a pilot parallel, pragmatic, stratified, randomised, open-label, single-blind, controlled study in an allocation ratio of 1:1. We planned to conduct this study in seven hospitals in Jakarta and Bekasi as described in our protocol [27], however we only received research permits from six hospitals. Due to low rate of recruitment, we added two primary care centres in Jakarta to the study.

Participants

Inclusion criteria

We included children aged six months to 12 years old with AOM, defined as current onset (within 48 hours) of AOM-relevant symptoms (e.g. earache, ear tugging/rubbing or irritability in non-verbal children). Otoscopic findings of acute inflammation (e.g. erythema) and middle ear effusion (e.g. bulging, air-fluid level) confirmed the diagnosis.

Exclusion criteria

We excluded children (1) with major and severe medical conditions (e.g. heart diseases, tuberculosis), (2) who were immunocompromised (e.g. HIV infection, under cancer treatment), (3) with congenital malformations and/or syndromes (e.g. cleft palate, Down syndrome), (4) with high risk of strongyloidiasis infections, (5) with ear ventilation tube(s), (6) who had been exposed to persons with varicella or active Zoster infection in the preceding three weeks without prior varicella immunisation or infection, (7) who had taken systemic (oral, injection) or topical steroids in the preceding four weeks, (8) who had taken antibiotics in the preceding two weeks, and (9) who were hypersensitive to prednisolone or prednisone, or other corticosteroids. Further details of the recruitment process including obtaining consent are in our protocol [27].

Study intervention arm

We gave prednisolone tablets (Lupred®5) at a daily dose of 1–2 mg/kg of body weight for five days, which was operationalised based on age: 10 mg/day for children aged six months to up to two years; 20 mg/day for children aged two up to six years; and 30 mg/day for children aged six to 12 years [28]. We provided liquid sweetener to make prednisolone more palatable. Children with mild AOM who were randomised to the intervention arm received prednisolone plus expectant observation, whilst those with severe AOM received prednisolone plus antibiotics (see Figure 1). Further details of administration and timing of study medication are described in our protocol [27].

Control arm

Children with mild AOM who were randomised to the control arm received expectant observation alone, whilst those with severe AOM received antibiotics alone (see Figure 1).

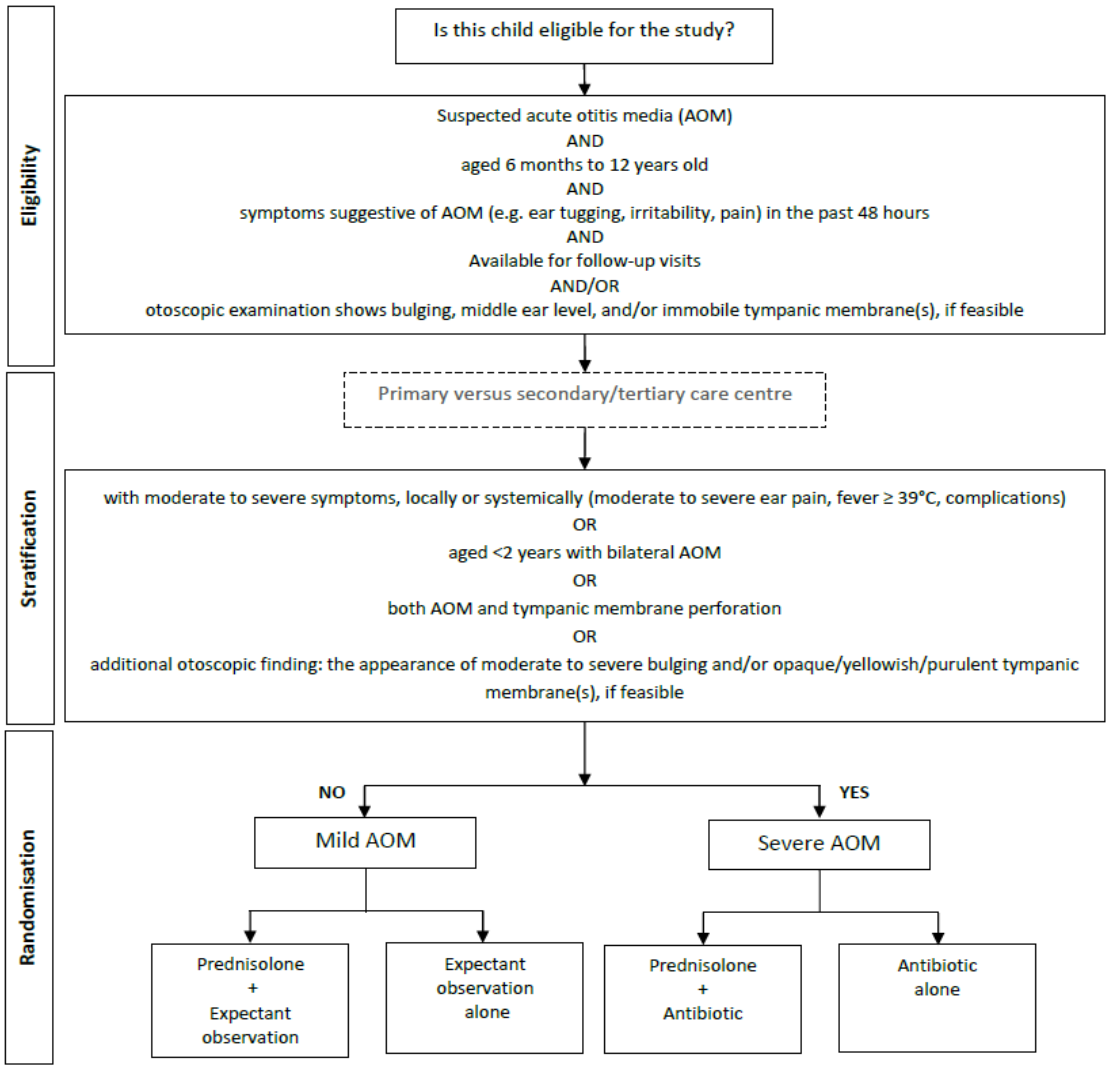


Figure 1. Flowchart of the study stratification and randomisation

Concurrent treatment

Physicians were able to prescribe medications for symptoms (e.g. analgesic, decongestant) as per their usual practice. The physicians were not able to prescribe oral corticosteroids.

Outcomes

For the first objective of assessing the feasibility of characteristics of our full RCT design and procedures, we measured four outcomes: (1) recruitment rates; (2) successful completion of the study procedures; (3) successful measurement of planned outcomes; (4) the experiences and barriers of participating healthcare personnel (i.e. physicians, nurses, audiologists, pharmacists) and parents/caregivers in measuring planned outcomes; (5) adherence to study visits and study medication; and (6) verification of the sample size calculation for the full RCT using pain measures in the control group.

For the second objective of assessing the mechanistic effect of corticosteroids in suppressing inflammation in the middle ear, we measured three outcomes: (a) change in MEE at various time points; (b) duration of MEE; and (c) correlation between ear pain and other symptoms with the changes in MEE at various time points.

Recruitment rate was defined as the proportion of consultations with potentially eligible children who provided their consent to be included in the study. We assessed this outcome monthly using a logbook completed by participating nurses and physicians.

The successful completion of the study procedures and outcome measures was defined as the proportion of participating healthcare personnel and parents/caregivers who were able to conduct study procedures and measure outcomes in order to obtain valid results. The study procedures were: (1) obtaining consent; (2) recruitment and stratification; (3) otoscopic assessment; (4) pain measures using Visual Analogue Scale (VAS) and Acute Otitis Media Severity of Symptoms (AOM-SOS) scale; (5) randomisation, treatment allocation, and prescription dispensing; (6) preparation, completion, compilation, and storage of case report forms (CRFs); (7) tympanometry examination and interpretation; (8) preparation and dispensing of study medication; and (9) completion of the symptom diary. These outcomes were measured using the logbook, case report form, and the symptom diary (Additional file 1. Case report forms).

For the assessment of the experience and barriers to measuring outcomes, we used a feedback form (see Additional file 1. Case report forms). Each question represented a study procedure and had five responses (‘very easy’, ‘easy’, ‘neutral’, ‘difficult’, and ‘very difficult’). We asked the healthcare personnel and parents to choose one response. We asked those who chose ‘difficult’ to choose obstacle(s) describing their experience during that procedure or measurement. They could choose more than one option or write their personal experience.

We assessed the adherence to study medication by identifying the proportion of children who took the study medication (prednisolone) for five days per protocol divided by all children in the prednisolone group. This outcome was measured using the symptom diary. The adherence to the study visit was assessed by identifying the proportion of children who came to follow-up visits at Day 3, Day 7, Day 30, and Day 90 per protocol divided by all children randomised to the study. This outcome was measured using the follow-up card, the consent form, and the symptom diary.

The verification of sample size for the full RCT was calculated by identifying the proportion of children with mild and severe AOM in the pilot study with ongoing pain represented as VAS score ≥ 5 mm, at Day 3, in the control group.

We assessed change in MEE at Day 3, Day 7, Day 30, and Day 90 by measuring static acoustic admittance (SAA), which is defined as ‘the amount of energy absorbed by the tympanic membrane and middle ear’. We assumed that a difference of 0.3 mmho was a minimum clinically important one for SAA [29].

For duration of MEE, we only conducted tympanometry at follow-up visits. We were not able to identify whether the effusion had persisted, disappeared, or reappeared between these visits. Therefore, we reported this as the proportion of children who had a complete resolution of MEE which is represented by a type A curve at follow-up visits. We used the modification of Jerger to classify the tympanogram curve types, as follows: (1) a type A curve indicating a normal middle ear; (2) type C curves including a C1 curve, which indicates a transition from a normal middle ear to an early MEE, and a C2 curve representing an early MEE; and (3) a type B curve, strongly indicating the presence of MEE or a definite MEE [30-33].

We assessed the correlation between ear pain and other symptoms (i.e. ear tugging, irritability, crying, lack of sleep, lack of appetite, loss of playfulness, fever) using VAS and AOM-SOS assessed by parents in the symptom diary with the changes in SAA at Day 3, Day 7, Day 30, and Day 90.

The planned primary outcome of the full RCT is the proportion of children with pain that has not reduced by the minimum clinically important amount (10 mm VAS) by Day 3 [34,35]. The secondary outcomes are: (1) the proportion of children with ongoing pain (VAS $\geq$ 5 mm) [36] at Day 1, 3, 5, 7, and 14; (2) reduction of pain intensity measured using VAS at similar time points; (3) reduction of overall symptoms measured using AOM-SOS at similar time points [37]; (4) reduction of overall pain duration; (5) complications related to AOM; (6) the proportion of children with mild AOM requiring antibiotics and those with severe AOM requiring second-line antibiotics; (7) AOM recurrence; (8) adverse effects; and (9) the adherence to study medication. For the VAS and AOM-SOS assessment, we used data from the symptom diary completed by the parents. As this is a pilot, we do not report here the primary outcome of the full RCT. However, we do report the first secondary outcome. Further details of data collection for the pilot and full RCT are described in our protocol paper [27].

Sample size

We did not formally determine the sample size for this pilot study. We included 60 children with AOM in our pilot study based on sample size calculation for the tympanometry sub-study [27]. Our feasibility survey demonstrated that it would require nine months including 3-month follow-up to recruit 60 children. We did not conduct an interim analysis due to the small sample size and short study duration.

Recruitment and stratification

For the full RCT, we plan to stratify children by clinical specialty or healthcare centre level (primary care or secondary/tertiary healthcare centres) and severity of AOM (mild or severe). As we intended to only include ENT specialists who worked at secondary/tertiary centres in this pilot study, we stratified children based only on AOM severity. Details on stratification criteria are in the protocol paper [27].

To help the recruitment and stratification process, including randomisation and tympanometry examination where necessary, we recruited and trained seven research assistants, including one

administrative assistant, to support the implementation of the study (RO, DN, IG, RA, RS, FR, VV).

Randomisation and allocation concealment

After confirmation of eligibility, and completion of the clinical examination, but prior to randomisation, physicians dispensed two prescriptions to the nurse. The first prescription was for general AOM medications (e.g. antibiotics, decongestants). The second one was for the study medication. The nurse then only dispensed the second prescription to patients who were randomised to the intervention arm. Further details of randomisation process, including the preparation, dispensing and central storage of study medication are in the protocol paper [27].

Blinding

The appointed nurses and patients or parents/caregivers were aware of the intervention allocation. The physicians and audiologists were blinded to the allocation [27]. At the primary care centre, the principal investigator (RR) and research assistants (RO, DN, IG, RA, RS, FR) conducted randomisation and tympanometry examination because of the limited availability of healthcare personnel for the study. Therefore, it was not possible to conceal allocation after randomisation. However, the research assistants were not involved in the treatment decisions and ensured the clinician was not aware of the intervention allocation.

Statistical methods

We report the outcomes of the pilot study (e.g. recruitment rate, the success and ability of study procedures and measures, adherence to study visits and medication) as proportions in percentages (n, %).

For the verification of sample size calculation, we used the proportion of the children in both mild and severe groups, and pain measures among the controls to update our calculation of failure rate of ongoing pain at Day 3. We did not change the assumed relative of risk on ongoing pain at Day 3, as the pilot results arise from a small sample.

For the clinical outcomes, since it was a pilot study and we did not want to reveal the result of the primary outcome of the proposed full RCT, we only report the proportion of children with ongoing pain (binary outcome) and reduction of pain and other symptom severity (continuous outcome) at: Day 1, Day 3, Day 5, Day 7, and Day 14. For clinical and tympanometry

continuous outcomes (i.e. pain and symptoms scores measured by VAS and AOM-SOS, SAA value), we conducted linear regression to determine the unadjusted and adjusted mean difference (MD), 95% confidence interval (CI), and the p values for the comparison between groups at Day 3 as a primary time point . The adjusted MD used the baseline result (equivalent to ANCOVA). Spearman's correlation coefficient was calculated to determine the correlation between ear pain using VAS and SAA values on the affected ear for unilateral AOM and the worst ear for bilateral AOM, as well as between other relevant symptoms using AOM-SOS and the similar SAA values. We used STATA 15.1 software for statistical analysis.

For clinical and tympanometry binary outcomes (i.e. the proportion of children with persisting pain of VAS $\geq$ 5 mm and those who had complete MEE resolution at various time points), we conducted chi-squared tests and reported relative risk (RR) and 95% CI for the comparison between groups. We presented the p values of the outcomes measured at Day 3 (primary time point). We used Fisher's exact test to determine statistically significant differences in effect estimates of binary outcomes between the prednisolone and control group where there were small event numbers (< 10 per variable cell).

For time to pain resolution, we identified the time point where children had resolution of pain (VAS < 5 mm) and presented these as a median, and then compared the median between the two groups using a Wilcoxon rank sum test.

Results

Recruitment

We screened 512 children with ear pain (22 February-30 November 2018) and 161 children (31%) were assessed using the eligibility criteria (see Figure 2). All physicians were able to confirm AOM using an otoscope. Sixty-two (38%) eligible children were stratified to mild and severe AOM. Thirty-one children were randomly allocated to the prednisolone group (8 mild and 23 severe AOM) and 31 children to the control group (7 mild and 24 severe AOM). Two children left the study before data collection at Day 3 resulting in 60 children (29 prednisolone versus 31 control group) were analysed for the planned primary outcome of the full RCT. The study was ended on February 2019 allowing for the 3-month follow-up of the last patient.

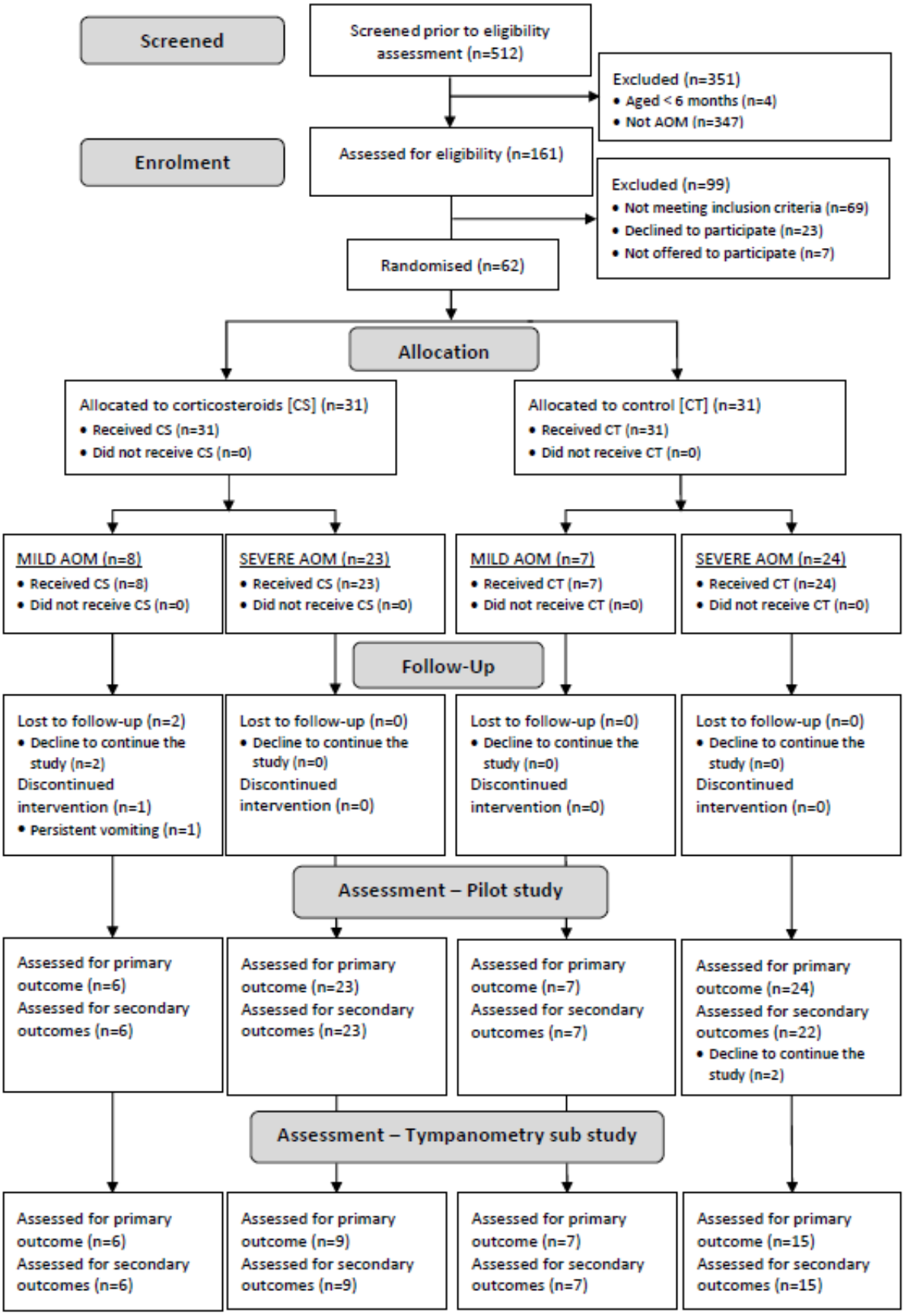


Figure 2. Study flowchart

Baseline data

The baseline characteristics between the two groups were similar in gender and had an age range of 61 to 73 months (see Table 1). There were more children in the control group whose parents had a low education level (primary and secondary education), were exposed to parental smoking (passive smoking), or received amoxicillin and amoxicillin/clavulanate and acetaminophen at baseline. Children in the prednisolone group were more likely to receive cefixime. Forty-seven per cent of the children were found to have hyperaemic tympanic membrane only on the otoscopic examination.

Table 1. Baseline and clinical characteristics of randomised children by treatment group.

Characteristics	Prednisolone (n=31)	Control (n=31)
Baseline characteristics		
Age (months) mean ± SD	60. 7 ± 32.2	73.2 ± 38.3
Sex - male (n; %)	15 (48)	18 (58)
Breastfeeding (n; %)	28 (90)	27 (87)
Breastfeeding until at least the first 6 months of life (n; %)	20 (71)	19 (70)
Child day care attendance (n; %)	1 (3)	1 (3)
Duration per week (hours) mean ± SD	50	35
Pre-school or school attendance (n; %)	21 (68)	20 (64)
Duration per week (hours) mean ± SD	4.9 ± 2.0	4.7 ± 2.0
Parental education (father)*		
Primary education (i.e. elementary school)	1 (3)	2 (6)
Secondary education (i.e. middle and high school)	13 (42)	17 (55)
Tertiary education (e.g. diploma, bachelor, masters)	16 (52)	11 (35)
Parental education (mother)*		
Primary education (i.e. elementary school)	0 (0)	2 (6)
Secondary education (i.e. middle and high school)	12 (39)	17 (55)
Tertiary education (e.g. diploma, bachelor, masters)	19 (61)	11 (35)
Pneumococcal vaccinations (n; %)	9 (29)	7 (23)
Influenzae vaccinations (n; %)	6 (19)	7 (23)
≥3 episodes of acute respiratory infections in the past year (n; %)	23 (74)	22 (71)
First episode of AOM	20 (64)	21 (68)
First episode of AOM at ≤2 years of age (n; %)	8 (26)	3 (10)
≥3 episodes of ear infection in the past year (n; %)	3 (10)	2 (6)
>3 children in one house (n; %)	0 (0)	0 (0)
Passive smoking (n; %)	14 (45)	20 (64)
Ear discharge (n; %)	11 (35)	8 (26)
Concomitant diseases (n; %)		

Characteristics	Prednisolone (n=31)	Control (n=31)
Allergic rhinitis	3 (10)	2 (6)
Bronchial asthma	0 (0)	1 (3)
History of atopy in the family	12 (39)	9 (29)
AOM lateralisation – unilateral (n; %)	20 (64)	18 (58)
Clinical characteristics		
Common cold	27 (87)	28 (90)
Nose abnormalities (e.g. oedema, discharge)	23 (85)	23 (82)
Tonsil abnormality (e.g. hyperaemic, oedema)	15 (55)	15 (53)
Throat abnormality (e.g. hyperaemic, oedema)	15 (55)	8 (28)
Diagnosis of AOM		
Confirmed by otoscope		
Hyperaemic tympanic membrane only	12 (39)	17 (55)
Hyperaemic tympanic membrane and other signs of inflammation/middle ear effusion†	23 (74)	21 (68)
Confirmed by otoscope and clarified by tympanometry‡	25 (86)	25 (86)
Initial antibiotic given (n; %)		
Amoxicillin	4 (13)	11 (35)
Amoxicillin/clavulanate	5 (16)	8 (26)
Cefixime	12 (39)	3 (10)
Cefadroxil	1 (3)	1 (3)
Trimethoprim/sulfamethoxazole	0 (0)	1 (3)
Clarithromycin	1 (3)	0 (0)
Other treatment given by doctors at initial visit (n; %)		
Acetaminophen	9 (29)	16 (52)
Nonsteroidal Anti-inflammatory Drugs	4 (13)	5 (16)
Decongestants and/or antihistamine	26 (84)	22 (71)
Cough medicine	18 (58)	14 (45)
Antibiotic ear drops	9 (29)	6 (19)
Nasal (topical) decongestant	6 (19)	2 (6)
Nasal corticosteroid	0 (0)	1 (3)
Vitamins or herbals	3 (10)	8 (26)
Ear diathermy	0 (0)	1 (3)
Inhalation	0 (0)	1 (3)
Others (e.g. mefenamic acid, nasal douching)	3 (10)	5 (16)
Tympanometry test (n; %)	29 (93)	29 (93)
Complete	15 (52)	18 (62)
Partial completion	0 (0)	6 (21)
Sufficient values for analysis	15 (52)	22 (76)
Type A	4 (27)	6 (27)

Characteristics	Prednisolone (n=31)	Control (n=31)
Type C1	2 (13)	4 (18)
Type C2	1 (7)	1 (4)
Type B (or flat)	8 (53)	11 (50)

*We could not obtain the information of father's (n=2) and the mother's education level (n=1); †A child with bilateral AOM may have two different otoscopic results (e.g. hyperaemic tympanic membrane only and hyperaemic tympanic membrane with other signs of inflammation/middle ear effusion); ‡Four patients did not undergo tympanometry examination due to: severe pain, not recommended by physicians due severe bulging, uncooperative child, and nurse forgot. Patients with tympanic membrane perforation were considered as confirmed by otoscope and tympanometry.

Numbers analysed

For the primary outcomes of the full RCT, we analysed 60 children at Day 3. For the secondary outcomes, we analysed 58 children (29 prednisolone versus 29 control group) as two more children left the study after data collection at Day 3. For the tympanometry sub-study, we conducted tympanometry examinations on 58 children (93%) and analysed 37 children (15 prednisolone versus 22 control group) who had sufficient tympanometry findings at both baseline and Day 3. We were not able to fulfil the sample size to 60 children due to difficulty in recruitment and budget constraints which prevented the extension of the recruitment period.

Outcomes and estimation

Recruitment rate

We collected logbooks from each study site to measure the recruitment rate. However, most nurses did not complete the logbook appropriately. The average recruitment rate was 38.5% of potentially eligible children (see Table 2). The main reasons for exclusion were: (a) onset > 2 days (24%); (b) lack of interest or reluctance of parents to participate (14%); and (c) prior intake of antibiotics/steroids (10%). Three sites did not contribute to patient recruitment because of no eligible cases. Only one private hospital contributed to the study recruitment. Therefore, we added two primary care centres to the study.

Table 2. Recruitment rates

Recruitment details according logbook	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Monthly Mean
Recruitment rate* (%)	0	48	33.3	44.4	33.3	66.7	40	40	35.7	20.7	38.5
Screened children with AOM	1	25	18	9	6	15	15	15	28	29	16.1

Recruited to the study	0	12	6	4	2	10	6	6	10	6	6.2
Did not meet study criteria	0	7	4	2	2	4	7	8	14	21	
Onset >2 days	0	4	3	2	1	3	4	4	7	10	
Prior antibiotic/steroid intake	0	3	1	0	0	1	1	2	4	8	
Chronic/ immunosupp disorders	0	0	0	0	0	0	2	0	0	0	
Unable for follow-up visits	0	0	0	0	1	0	0	2	3	3	
Declined to participate	1	5	6	3	1	1	0	1	4	1	
Not offered participation	0	1	2	0	1	0	2	0	0	1	

*recruitment rate = children with AOM aged six month to 12 years who were recruited into the study divided by all children with AOM aged six months to 12 years who were being assessed for the study by participating physicians.

The successful completion of the study procedures and outcome measures

Prior to the study, we provided training to 66 physicians (i.e. ENT specialists, GPs, paediatricians), 39 nurses, 35 pharmacists, and 6 audiologists. During the training, we coached and assisted them in conducting all study procedures and measures per protocol.

Twenty-three of 85 parents/caregivers of eligible children (27%) declined to participate in the study (see Table 2). All physicians (100%) successfully recruited and stratified eligible children based on their AOM severity, performed an otoscopic assessment, and measured pain and other relevant symptoms using VAS and AOM-SOS, and reported the findings as self-reporting assessment in the CRF. All eligible children were successfully randomised and allocated to their randomised intervention by nurses/research assistants. All patients had the study medication prescriptions dispensed as per protocol. All nurses were able to appropriately prepare, compile, and store the CRF. All audiologists successfully performed tympanometry examination. However, there were incomplete values caused by lack of sensitivity of tympanometry. One of 31 study medication packages (3%) was not dispensed by the pharmacist, which had to be home delivered by the researcher (RR).

One hundred per cent of symptom diary data was completed for analysis. However, only 60% of parents/caregivers were able to complete the symptom diary per protocol, which required us to collect data and clarify unclear responses by interviewing 25 parents retrospectively (see Table 3). We regularly checked the completion of the symptom diary of: Day 0 to 3 at the first

follow-up visit (Day 3) and Day 4 to 7 at the second visit (Day 7), and after the diary collection at Day 14. We expected this strategy may reduce recall bias. We interviewed the parents directly during the consultation at the follow-up visits and at the follow-up by phone at Day 14.

Experiences and barriers to measuring planned outcomes of the full RCT.

We measured this outcome using a feedback form. We only invited physicians and nurses who recruited patients or were involved in data collection for at least two patients to provide feedback. We obtained feedback from 15 ENT specialists (15/51; 29%), six GPs (6/9; 67%), 16 nurses (16/39; 41%), six pharmacists (6/35; 17%), and four audiologists (4/6; 67%).

Most ENT specialists and GPs rated obtaining consent from parents, recruiting and stratifying patients into the study, and using otoscopes as 'easy'. The common obstacles were: (1) reluctance to participate due to the term 'research' in the consent form; (2) lengthy time to deliver extensive study information; (3) time constraints due to the need for an increased appointment length and pressure of patient numbers; and (4) a complex eligibility form. General practitioners found using an otoscope was challenging in some patients due to the narrowness of ear canals and uncooperative children. Most ENT specialists (73%) rated completing the CRFs as 'easy', whilst most GPs rated this as 'neutral' (50%). The ENT specialists recommended simplification of the CRFs.

Most ENT specialists and GPs rated VAS (71% and 75%, respectively) and AOM-SOS (85% and 100%) as 'easy', although more information on pain description was required. They suggested using a facial scale to measure pain. They found AOM-SOS was suitable to assess pain in young children.

Most nurses rated the randomisation process and CRF compilation, preparation and storing as 'easy', and rated treatment allocation and prescription dispensing as 'neutral'. They found obstacles when accessing the randomisation website due to complicated access steps and unstable internet connection. They also found these were time-consuming, particularly in terms of randomisation and CRF compilation, which were not always feasible due to workload. Most nurses contacted the 24-hour call centre for assistance in the randomisation and recruitment process.

The pharmacists and audiologists rated the preparation and dispensing of study medication, and tympanometry examination as ‘very easy’ to ‘easy’. We also obtained feedback from our research assistants (n = 6) who conducted tympanometry examination in primary care centre. Only one rated this as ‘difficult’ due to the narrowness of ear canals.

We obtained feedback from parents regarding the completion of the symptom diary (see Figure 3). The majority of parents rated VAS (47%), AOM-SOS (71%), and the completion of symptom diary (62%) as ’easy’. Parents preferred to use a numeric pain scale.

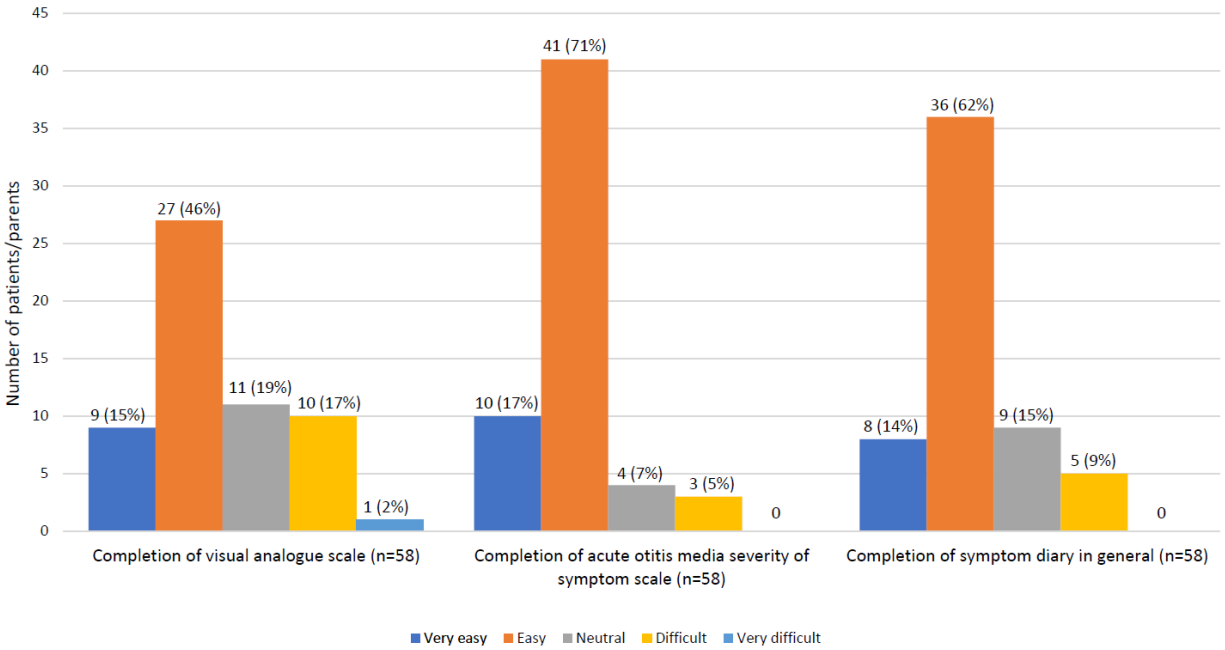


Figure 3. Parents’ experience in measuring planned outcomes for the main study

Adherence to study visits and study medication

Fifty-eight children completed all follow-up visits and four children left the study (see Table 3). We visited homes of those who were not able to come for their follow-up visits. During this visit, we did not prescribe any medication and recommended they visit the hospital/primary care centre for any concerning condition (e.g. worsening AOM, complications).

Four children received additional oral corticosteroids: one from a participating physician for AOM and three children received it from other physicians for asthma, prolonged cough due to allergy, and sore throat. All received this after measurement of the primary outcome (see Table 3).

Table 3. The adherence to the study.

Adherence to the study	Prednisolone (n=31)	Control (n=31)
Not compliant to the completion of symptom diary		
No data after baseline for primary outcome analysis	2	0
Data collected retrospectively by interview	4	13
Unclear responses clarified by interview	5	3
Not compliant to study medication*		
Missed one dose, but taken on the next day	1	-
Vomited constantly and stopped the study medication	1	-
Took half of dose, vomited <30 minutes) and took another half of dose	1	-
Took medicine in the afternoon (not in the morning)	2	-
Not compliant to the follow-up visits		
Delayed timing of follow-up visit	3	3
Left study	2	2
Additional interventions		
Received additional oral corticosteroids	3†	1‡
Received intervention of co-medication from study investigator	2	5

*Nine patients did not complete diary, but the adherence confirmed by interview; †At Day: 10, 12, and 60; ‡At Day 7.

Interference by research investigator.

Due to the lack of available second-line antibiotics and other medications in primary care centres, the principal investigator (RR), who was not blinded to the intervention allocation, provided several medications to seven patients: second-line antibiotics (4/62; 6%); ibuprofen (4/62; 6%); combined decongestant-antihistamine (6/62; 10%); cough syrup (5/62; 8%); topical decongestant (4/62; 6%); and nasal saline drops (1/62; 2%). More children in the control group received interference, since most children in primary care centres were randomly allocated to this group by chance.

Verification of sample size calculation for the full RCT.

Based on our original sample size calculation, we need to enrol 760 children with AOM. We estimated, based on data by Rovers et al. [38], that there would be 35% of the total sample of children with AOM in the severe group, of which 57.5% would have ongoing pain at Day 3 in the control group. However, in our study, 78% of our total sample was in the severe group with

risk of ongoing pain (≥ 5 mm VAS) at Day 3 in control group of 42%. Of the children with mild AOM, 57% in the control group had ongoing pain at Day 3. The average proportion of children with ongoing pain when combining the mild and severe groups was 45.2%. With our original assumption of 0.70 risk ratio with steroids, we will need to study 201 experimental and 201 control subjects to be able to reject the null hypothesis with probability (power) 0.8 and type I error probability of 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. With a 10% allowance for dropouts, the total sample size becomes 444.

There is a notable difference in the sample size estimation between our original sample size and our pilot study (see Table 4). The calculation of our original sample size was based on assumptions from a meta-analysis of studies conducted in developed countries. Our updated sample size using the pilot study results demonstrated that we need a smaller sample size for the full RCT if it is conducted in an urban setting in a developing country. The sample size may change if the study is conducted in different settings or countries. We are therefore presenting our assumptions for the sample size calculation for a clinical trial conducted in different settings (see Table 4).

Table 4. Sample size assumptions for a clinical trial of corticosteroids for AOM conducted in different settings.

Proportion of children	Original assumption [38]*	Middle scenario	Pilot observed result†
With severe AOM	35%	56%	78%
With severe AOM AND ongoing pain	57.5%	50%	42%
With mild AOM	65%	43%	22%
With mild AOM AND ongoing pain	36%	46%	57%
With severe and mild AOM AND ongoing pain	31.6%	38.4%	45.2%
Sample size calculation‡	760	570	444

*From a meta-analysis of studies conducted in developed countries; †Our pilot study was conducted in a developing country, urban setting; ‡The sample size includes a 10% allowance for dropouts.

Change of middle ear effusion (MEE).

We found no difference in MEE change represented by SAA between the prednisolone and control groups at: Day 3 (MD 0.04 mmho, 95% -0.07 to 0.16), Day 7 (MD 0.07 mmho, 95% -0.06 to 0.19), Day 30 (MD -0.05 mmho, 95% -0.19 to 0.09), and Day 90 (MD 0 mmho, 95% -

0.14 to 0.14). Consistent results were found after adjustment for the baseline results (see Table 5). All differences were well below the minimum clinical important difference of 0.3 mmho.

Table 5. Static acoustic admittance values in the affected (unilateral AOM) or the worst ear (bilateral AOM).

Static acoustic admittance: mmho mean ± SD	Prednisolone (n=15)	Control (n=22)	Unadjusted mean difference	*p value*	Adjusted mean difference*	*p value*
Day 0 (Visit 1)	0.19 ± 0.13	0.24 ± 0.22	-0.05 (-0.18, 0.08)			
Day 3 (Visit 1)	0.26 ± 0.15	0.22 ± 0.17	0.04 (-0.07, 0.16)	0.43	0.07 (-0.02, 0.16)	0.13
Day 7 (Visit 2)	0.32 ± 0.15	0.25 ± 0.20	0.07 (-0.06, 0.19)		0.08 (-0.03, 0.20)	
Day 30 (Visit 3)	0.32 ± 0.18	0.37 ± 0.22	-0.05 (-0.19, 0.09)		-0.03 (-0.16, 0.10)	
Day 90 (Visit 4)	0.41 ± 0.18	0.41 ± 0.22	0 (-0.14, 0.14)		0.02 (-0.11, 0.16)	

*Adjusted for the baseline static acoustic admittance value.

Duration of middle ear effusion.

Although the confidence interval was very wide, there was no difference in the proportion of children who had complete resolution of MEE between the prednisolone and control groups at: Day 3 (RR 1.76, 95% CI 0.65 to 4.73); Day 7 (RR 1.47, 95% CI 0.71 to 3.04), Day 30 (RR 1.07, 95% CI 0.57 to 2.00), and Day 90 (RR 1.17, 95% CI 0.80 to 1.72). We also identified any improvement of curve type from the baseline and previous results. Improvement was defined as an improvement from type B curve to type C2, C1, or A curve; or from type C2 curve to type C1 or A curve; or type C1 to A curve; or persisting type A curve. Table 6 shows the tympanometry curve improved compared to the baseline in more children in the prednisolone group at Day 7 (RR 1.76, 95% CI 1.04 to 2.97).

Table 6. Tympanometry finding in the affected (unilateral AOM) or the worst ear (bilateral AOM).

Tympanometry findings	Prednisolone (n=15)	Control (n=22)	Effect estimate (relative risk)	*p value*
Complete middle ear effusion resolution* (n, %)				
Day 3 (Visit 1)	6 (40)	5 (23)	1.76 (0.65, 4.73)	0.29
Day 7 (Visit 2)	8 (53)	8 (36)	1.47 (0.71, 3.04)	
Day 30 (Visit 3)	8 (53)	11(50)	1.07 (0.57, 2.00)	
Day 90 (Visit 4)	12 (80)	15 (68)	1.17 (0.80, 1.72)	

Improvement of curve type from baseline visit† (n, %)				
Day 3 (Visit 1)	7 (47)	7 (32)	1.47 (0.65, 3.32)	0.49
Day 7 (Visit 2)	12 (80)	10 (45)	1.76 (1.04, 2.97)	
Day 30 (Visit 3)	10 (67)	14 (64)	1.05 (0.65, 1.69)	
Day 90 (Visit 4)	14 (93)	16 (73)	1.28 (0.96, 1.71)	
Improvement of curve type from previous visit‡ (n, %)				
Day 3 (Visit 1)	7 (47)	7 (32)	1.47 (0.65, 3.32)	0.49
Day 7 (Visit 2)	9 (60)	9 (41)	1.47 (0.76, 2.81)	
Day 30 (Visit 3)	9 (60)	13 (59)	1.01 (0.59, 1.74)	
Day 90 (Visit 4)	13 (87)	15 (68)	1.27 (0.89, 1.80)	

*Complete resolution is defined as a type A curve in tympanometry examination; †Improvement of curve type is defined as an improvement from type B curve to type C2, C1, or A curve; or from type C2 curve to type C1 or A curve; or type C1 to A curve; or persisting type A curve at particular time point compared to the baseline; ‡Improvement of curve type is defined as an improvement from type B curve to type C2, C1, or A curve; or from type C2 curve to type C1 or A curve; or type C1 to A curve; or persisting type A curve at particular time point compared to the previous visit.

Correlation between ear pain and other relevant symptoms and the change of MEE.

We expected there would be a strong negative correlation between lower VAS (no or less pain) scores or lower AOM-SOS scores (no or less AOM-relevant symptoms) and higher values of SAA (no middle ear effusion), particularly at early timepoints. However, our analysis demonstrated only a small correlation between pain and other AOM-relevant symptoms and MEE at Day 3 and 7 (see Figure 4), as well as later (Day 30 and 90) (see Appendix 1).

[129]

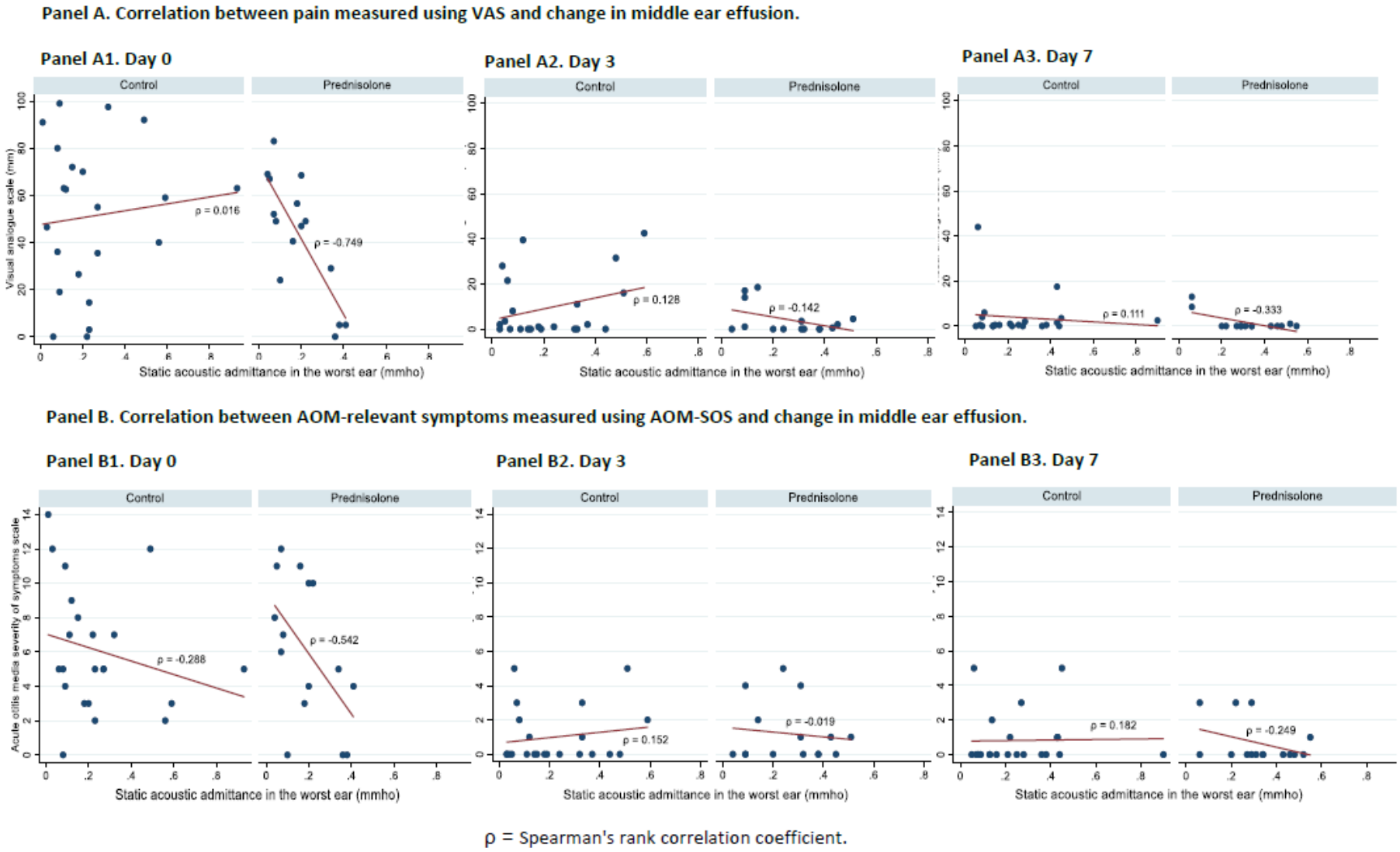


Figure 4. Correlation between pain or AOM-relevant symptoms and change in middle ear effusion]

For clinical outcomes of this pilot study, we found prednisolone reduced pain severity at Day 3 by 7 mm (MD -7.37, 95% CI -13.36 to -1.39, p = 0.018). Although it was less than 10 mm (the minimum clinical important difference), the CI included 10 mm which indicates there may be a clinically important reduction in pain severity. There was no statistically significant difference in the proportion of children with ongoing pain at Day 1, 3, 5, 7, and 14 (see Appendix 1). Neither was there a difference between groups in reduction of pain severity at these timepoints except Day 3. The results remained consistent after being adjusted for the baseline pain score (ANCOVA).

Harm

Regarding harm or adverse events (AEs), there were more children in the prednisolone group experienced drowsiness (RR 1.77, 95% CI 1.11 to 2.81, p = 0.016), Table 7. This can be translated as for every three paediatric AOM patients who received oral prednisolone, one additional patient experienced drowsiness (number needed to harm/NNTH of 3). However, there were no serious AEs of any kind attributed to study medication. There were no significant differences in the proportion of children experiencing other AEs between two groups, including those AEs commonly attributed to short-course oral corticosteroids use such as gastrointestinal problems (e.g. nausea, vomiting, diarrhea). We found one child in the prednisolone group who had microcytic hypochromic anemia at Day 6 based on low haemoglobin and serum iron counts. He was referred to a paediatrician who then confirmed this was most likely caused by iron deficiency and not by steroid intake.

Table 7. Adverse events in the study.

Adverse events	**Prednisolone group (n=31)**				**Control (n=31)**			
	No pts*	**Day 1-3**	**Day 4-7**	**Day 8-14**	**No pts***	**Day 1-3**	**Day 4-7**	**Day 8-14**
Increased appetite	**18**	11	15	17	**17**	9	10	7
Increased urine volume	**11**	8	9	7	**14**	12	7	4
Weight gain	**13**	5	6	6	**11**	4	4	10
Gastritis	**2**	3	2	0	**4**	2	0	0
Nausea	**6**	4	1	0	**7**	5	4	1
Vomiting	**5**	3	0	0	**3**	3	1	1
Diarrhea	**2**	3	1	1	**4**	1	0	0
Drowsiness	**23**	14	9	6	**13**	16	10	5
Anxiety	**4**	3	3	3	**6**	3	1	1

Headache	**4**	1	0	1	**6**	7	2	3
Skin rash	**3**	0	1	0	**0**	2	0	0
Candidiasis	**3**	2	1	0	**1**	1	0	0
Dry mouth	**7**	5	4	0	**6**	6	3	1
Sleep disturbance	**17**	5	5	3	**10**	9	1	0
Others	**1**	0†	1	0	**0**	0	0	0
Serious adverse effects	**0**	0	0	0	**0**	0	0	0

*Total number of patients having the adverse event during the first two weeks; †Patient was detected to have anemia at day 6 (no baseline Hb count was identified) at the primary care centre and was referred to paediatrician.

Pts: patients.

Sensitivity analysis

Due to interference of the principal investigator who was not blinded to study medication allocation, we conducted a sensitivity analysis by excluding the children who received interference. This did not change the results.

Discussion

Our pilot study met our two key objectives related to the feasibility of the full-size RCT and mechanistic effect of corticosteroids on MEE. We found that less than 40% of screened children were recruited. Most physicians and parents rated study procedures as ‘neutral’ to ‘easy’. However, most healthcare personnel found time constraints due to workload as their most common obstacle in the study. The sample size needed to power a full randomised controlled trial is lower than anticipated. Most children completed the study (97%), and a minority received concomitant oral corticosteroids and other co-treatments from an unblinded researcher. There is the potential that corticosteroids may reduce pain severity at Day 3 and improve tympanometry curve by Day 7. We found only a small correlation between the change in MEE and pain and other AOM-relevant symptoms. We also found drowsiness as the most common side effect of oral corticosteroid.

There were several limitations of this pilot study. Our recruitment rate was low and similar (38.5%) to other studies conducted in developing countries [39]. This could be because we started recruiting at hospital centres, but well-implemented national coverage insurance required patients to access healthcare services via primary care centres. It could also be due to: (1) low research awareness/interest among physicians, nurses, and patients [40]; (2) workload

of physicians and nurses; and (3) cultural factors (e.g. patients seeking family/relatives' consent to participate in research, and insufficient clinical trials facilities [40]. To improve recruitment, future studies could: (1) recruit from more primary care centres; (2) provide incentives for participating healthcare personnel despite insufficient evidence of effects on recruitment rate [41]; and (3) simplify the study process (simplifying and improving the layout of CRFs and symptom diary and allocating research assistants to support study procedures including randomisation).

We could not provide a matched placebo control. Parents' subjective responses to pain assessment could have been biased by this, as they knew which treatment their child received. However, we plan to use a placebo in the full RCT where we will involve an independent specialised drug manufacturer to provide a placebo that is similar in form and taste with oral prednisolone.

Four children received additional oral corticosteroids. Although we asked parents to contact us before they sought consultation from other physicians for any relevant or other concurrent conditions, this was not sufficiently implemented. Therefore, for the full RCT, we will provide a handy information card that provides detailed information about the study, including medication that should not be given. This card should be shown to any physicians that the parent consults.

Imbalanced randomisation meant that there were more children in the control group who had low parental education level, were exposed to parental smoking, and received amoxicillin and acetaminophen compared to those in the prednisolone group. One potential contributing factor was that, by chance, most children in the control group were recruited from the primary care centres. Out of 31 children in the control group, 13 were recruited from the primary care centres (55%) and out of 31 children in the prednisolone group, only six were recruited from primary care centres (19%). Low parental education level may be associated with higher rates of passive smoking in the control group. This was supported by evidence showing education attainment and length of education negatively correlated with smoking behaviour [42]. Parental smoking has been identified as a strong risk factor for AOM [43-45]. First line antibiotics for AOM and analgesics in primary care centres in Indonesia are amoxicillin and acetaminophen [15]. This is consistent with the antibiotic recommended for AOM in guidelines, but at a lower dose (50 mg/kg body weight/day) [15]. This chance imbalance in randomisation will likely be reduced

by stratification on the type of healthcare facility (primary versus secondary/tertiary care centre).

The last limitation was missing tympanometry values, which was caused by the inability of tympanometry to detect key values (i.e. SAA, middle ear pressure) in some severe cases of MEE. However, this problem was detected after several incomplete test values which resulted in missing data from several cases. Despite this, given the lack of clinical benefit of this examination in AOM cases, the need of specific skills and facilities, and cost, we do not intend to include the tympanometry measurement in the full RCT.

We also found positive impacts of this study. The first strength of this study is its ability to identify potential issues particularly in the recruitment and data collection which allows us to modify study procedures and strategies for a successful implementation of the full RCT [46]. Secondly, we also believe this pilot study has introduced a clinical trial to healthcare personnel at several levels of healthcare service in Indonesia. We expect this will trigger their interest in research since they now have some knowledge and experience in conducting a clinical trial.

Our original primary outcome was the proportion of children with ongoing pain that has not reduced by the minimum clinically important amount (VAS score of 10 mm) by Day 3. However, our pilot study demonstrated that the majority of the children had their pain significantly improved at Day 3. Therefore, we will change the primary outcome in the main RCT to be the proportion of children with persisting pain (defined as the VAS score greater than 5 mm). We will retain the secondary outcome, that is the reduction of pain intensity using VAS, which will allow us to identify the effectiveness of oral prednisolone to improve pain by the previously-defined minimum clinically important amount.

As we included different levels of healthcare service in several districts in Jakarta in the pilot study, we are confident that it is feasible to conduct the full RCT in other cities in Indonesia, particularly on Java. Training prior to the trial customised to education level of healthcare personnel is crucial. The availability of an otoscope will be a potential limitation for a large-scale RCT.

This study also showed that the incidence of severe AOM (47/62; 76%) was higher compared to other trials referenced in this study that were mainly conducted in developed countries. If a

large RCT is conducted in Indonesia or other developing countries with similar AOM characteristics, then it will predominantly evaluate the effects of oral corticosteroids as an addition to antibiotics.

Decongestants and/or antihistamines were commonly prescribed at baseline consultation. Most AOM patients experienced symptoms of the common cold which could explain this finding. Evidence shows the combination of decongestants and antihistamine is beneficial for general recovery in adults and older children with common cold, but not in young children (age < 5 years) [47]. Regarding its effects for AOM, decongestants and/or antihistamines have only a modest benefit in reducing the risk of persistent AOM in two weeks with significant adverse events overweighting the benefits [19].

We re-introduced the use of pain assessment tools (i.e. VAS and AOM-SOS) which have not been routinely used in the management of children with AOM in our clinical setting. Most parents assessed their children's pain by observation. Only few older children (5/62; 6%) did a self-rated pain assessment.

We also found that most parents and physicians preferred to use a numeric or facial pain scale. One of the commonly used self-report numeric scales for acute pain is the 11-point Numeric Rating Scale (NRS-11). Children, particularly aged 6 years and older, determine their pain intensity by choosing a number between 0 (representing 'no hurt') and 10 (representing 'the worst hurt') scale [48,49]. For facial pain scale, a Faces Pain Scale-Revised (FPS-R) was recommended as a self-report acute pain scale for children aged 7 years and older. It consists of six faces ranging from 'no pain' to 'very much pain', where each face was represented by numbers of 0-2-4-6-8-10 [48,50]. However, since there was no strong evidence supporting the recommendation of any particular parent-report pain assessment for paediatric population with acute pain, we still consider it appropriate to use VAS and AOM-SOS for the full RCT. This pilot study also verified that these pain assessment tools were successfully implemented by the parents in assessing pain.

We did not find clinically significant benefits of tympanometry examination for the management of AOM. It was costly and difficult to implement in children experiencing pain. Evidence demonstrates that only certain children may be at risk of prolonged MEE resolution (children with AOM aged < 2 years or, children with recurrent AOM). Therefore,

tympanometry examination should be prioritized for those children and not to be generalised for all AOM cases [9,51]. We will further investigate any prognostic factors and characteristics of our study participants in the tympanometry sub-study that may influence the improvement or prolongation of MEE.

We found drowsiness as the most common side effect of oral corticosteroid, which is consistent with AEs related to a short-term use of oral corticosteroids in other studies [21,26]. However, this requires further investigation since more children in the prednisolone group received decongestants and/or antihistamines, and drowsiness has been identified as common side effect of decongestants and/or antihistamines with risk up to eight-fold of risk in the treatment group [19,52,53].

Compared to other feasibility interventional studies, our pilot study had similar recruitment issues which required additional recruitment time and modification of the recruitment strategy [54]. Our study had a lower recruitment rate compared to other feasibility studies [55]. However, like other studies, our pilot study had a low rate of incomplete outcome data (6%) [54].

Conclusions

Our pilot study shows it is feasible to conduct a large, pragmatic, randomised, double-blind placebo- controlled trial. However, several modifications should be made to improve feasibility: simplifying study procedures, improving the layout of CRF and symptom diary, recruiting through primary care centres, stratifying children based on severity and healthcare centre level, and the use of placebo as a control. We will use VAS and AOM-SOS as pain assessment tools since there is no strong evidence recommending a particular parent-report assessment tool for children with acute pain. The sample size required is less than we anticipated due to the high proportion of severe AOM cases, and it is not necessary to use tympanometry for a future trial. Based on the findings and results from this pilot study, we modified our protocol for the full RCT (see Appendix 2).

Our clinical results do not rule out the benefit of oral corticosteroids for AOM. However, the signal of its benefits is small. We also identified drowsiness as one side effect of a short-term us of oral corticosteroids, with no excess of other AEs commonly attributed to short-course oral corticosteroids use (i.e. nausea, vomiting, diarrhea) found. Therefore, our pilot study confirms

the importance of conducting our planned full RCT to assess the actual effects, both benefits and harm, of oral corticosteroids for children with AOM.

List of abbreviations

AE: Adverse event; AOM: Acute otitis media; AOM-SOS: Acute Otitis Media Severity of Symptoms scale; ARI: Acute respiratory infection; BUHREC: Bond University's Human Research Ethics Committee;

CI: Confidence interval; CRF: Case report form; ENT: Ear, Nose, and Throat; FPS-R: Faces Pain Scale-Revised; GP: General practitioner; HIV: Human immunodeficiency virus; MD: Mean difference; MEE; Middle ear effusion; Pts: Patients; NRS-11: 11-point Numeric Rating Scale (NRS-11); P: P-value; RR: Relative risk; RCT: Randomised controlled trial; SAA: Static acoustic admittance; VAS: Visual analogue scale.

Declarations

Ethics approval and consent to participate

Our study protocol was reviewed and approved by the Ethics Committee Faculty of Medicine Universitas Indonesia (No. 852/UN2.F1/ETIK/2017 and Amendment No. 1088/UN2.F1/ETIK/X/2017) and the Bond University Human Research Ethics Committee (BUHREC) Australia (No. 16151 and Amendment No. 16208). We also received approval for conducting clinical research from the One Stop Integrated Service Agency Province of DKI Jakarta (No. 0204/AF.1/31/-1.862.9/2017) and the Training and Research divisions at each participating hospital. Prior to the recruitment and randomisation process, we provided the information sheet and obtained consent from the parent(s) or legal guardian of patients. Children aged 12 years had to provide their consent to participate in the study. The person who delivered the consent also provided their signatures on the consent form, stating that they had provided information and opportunity for potential participants to understand and raise relevant questions to the study. We ensured the consent process is free of coercion. As the study participation was voluntary, we emphasised their rights to withdraw from the study at any time without any consequences, particularly on the quality of their healthcare services.

Consent for publication

Not applicable.

Availability of data and materials

Our protocol is published in BMC Pilot and Feasibility Studies [27] and also can be accessed at https://research.bond.edu.au/en/publications/oral-prednisolone-for-acute-otitis-media-in-children-opal-study-a. The datasets generated and/or analysed during the current study are not publicly available because this is a pilot study which the clinical results could be misinterpreted. However, they are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research is supported by an Australian Government Research Training Program Scholarship and funded by the Australian National Health and Medical Research Council (NHMRC) [#1044904] as part of the Centre for Research Excellence in Minimising Antibiotic Resistance for Acute Respiratory Infections (CREMARA) and the Advance Women's Academic Fund Maternity funding [WAF-7026811-298]. These funding bodies had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Authors' contributions

RWR and EMB contributed in the study design, conception, planning, implementation strategy, data analysis and interpretation. AMC and CDM contributed in the study design, conception, planning, and implementation strategy. EDS and YP contributed in data collection and management, and recruitment strategy. WN contributed in obtaining research permits, data collection and management, and recruitment strategy. RWR, EDS, and YP also contributed in the interpretation of tympanometry results in the primary care centre. All authors have read and approved the final manuscript.

Acknowledgements

We thank Professor Dr. Sudigdo Sastroasmoro, Dr. Arie Sulistyowati, and Siti Rizny F. Saldi for their support and feedback in the implementation of the study. We also thank Professor Dr. Paul Glasziou as a Director of Institute for Evidence-Based Healthcare, Bond University, Queensland, Australia, and Professor Dr. Siti Setiati as a Director of Clinical Epidemiology and Evidence-Based Medicine Unit Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia for their support in the implementation of the study; the Directors, Head

of Departments of Otorhinolaryngology, Head and Neck Surgery, doctors, nurses, audiologists, and pharmacists at Dr. Cipto Mangunkusumo Hospital, Persahabatan General Hospital, Gatot Subroto Army Hospital, Proklamasi Ear, Nose, and Throat Centre (Proklamasi), Antam Medika Hospital, Islamic Hospital Cempaka Putih, Kemayoran and Pulogadung Primary Care Centres; Vonny Veronica, Dr. Rizki Ovianti, Dr. Dimas Nugroho, Dr. Redhafini Azizah, Dr. Ibrena Ginting, Dr. Rantung Salinas, Dr. Fajri Rozi for their hard work in assisting the study; and Neil Roberts, Student Learning Support, Bond University, for the assistance with proofreading.

References:

1. Chaw, PS, Höpner, J, Mikolajczyk, R. The knowledge, attitude and practice of health practitioners towards antibiotic prescribing and resistance in developing countries—A systematic review. J Clin Pharm Ther. 2018; 43: 606-613.
2. World Health Organization: Global action plan on antimicrobial resistance. World Health Organization. 2015; http://www.who.int/iris/handle/10665/193736.
3. Costelloe C, Metcalfe C, Lovering A, ndrew, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096.
4. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2015; doi: 10.1002/14651858.CD000219.pub4.
5. McDonagh MS, Peterson K, Winthrop K, Cantor A, Lazur BH, Buckley DI. Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review. Journal of International Medical Research. 2018;46(8):3337-3357.
6. Choez XS, Acurio MLA, Sotomayor REJ. Appropriateness and adequacy of antibiotic prescription for upper respiratory tract infections in ambulatory health care centers in Ecuador. BMC Pharmacology and Toxicology. 2018;19:46.
7. Teng CL. Antibiotic prescribing for upper respiratory tract infection in the Asia-Pacific region: a brief review. Malays Fam Physician 2014;9(2):18-25.
8. Pudjiarto P, Kurniawan YS, Kresnawati W. Irrational prescribing pattern for children with upper respiratory tract infection (URTI) in Indonesia. Paper presented at: Third International Conference for Improving Use of Medicines: Informed strategies, effective policies, lasting solutions; November 14-18; Turkey 2011.

http://apps.who.int/medicinedocs/documents/s21782en/s21782en.pdf. Accessed May 27, 2019.

9. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. Clinical practice guideline: the diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964–e999.
10. Liese JG, Silfverdal SA, Giaquinto C, Carmona A, Larcombe JH, Garcia-Sicilia J, et al. Incidence and clinical presentation of acute otitis media in children aged <6 years in European medical practices. Epidemiol Infect. 2014;142:1778–1788.
11. McCullough AR, Pollack AJ, Hansen MP, Glasziou PP, Looke DFM, Britt HC, et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. Med J Aust. 2017;207(2):65–69.
12. McGrath LJ, Becker-Dreps S, Pate V, Brookhart MA. Trends in Antibiotic Treatment of Acute Otitis Media and Treatment Failure in Children, 2000–2011. PLoS ONE. 2013;8(12): e81210.
13. Sigurðardóttir NR, Nielsen ABS, Munck A, Bjerrum L. Appropriateness of antibiotic prescribing for upper respiratory tract infections in general practice: Comparison between Denmark and Iceland. Scand J Prim Health Care. 2015;33(4):269-274.
14. Hansen MP, Jarbol DE, Gahrn-Hansen B, Christensen DR, Munck A, Ryborg CET, et al. Treatment of acute otitis media in general practice: quality variations across countries. Family Practice. 2012;29:63-68.
15. Ministry of Health Republic of Indonesia. Clinical practice guidelines for clinicians in primary healthcare centres. Jakarta: Ministry of Health Republic of Indonesia; 2014. Regulatory No. 5 year 2014.
16. Otology Working Group of Indonesian Otorhinolaryngologist Head and Neck Surgeon Society. Guidelines of Ear, Nose, and Throat Diseases in Indonesia. Jakarta: Indonesian Otorhinolaryngologist Head and Neck Surgeon Society; 2007.
17. Ministry of Health Republic of Indonesia. General guideline for antibiotic use. Jakarta: Ministry of Health Republic of Indonesia; 2011. Regulatory No.2406/MENKES/PER/XII/2011.
18. Djawaria DPA, Setiadi AP, Setiawan E. Questionnaire development and identification of factors contributing to non-prescription antibiotic selling behavior in Surabaya community setting. JMPF. 2018;8(3):105-118.
19. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database Syst Rev. 2008; doi: 10.1002/14651858.CD001727.pub4.

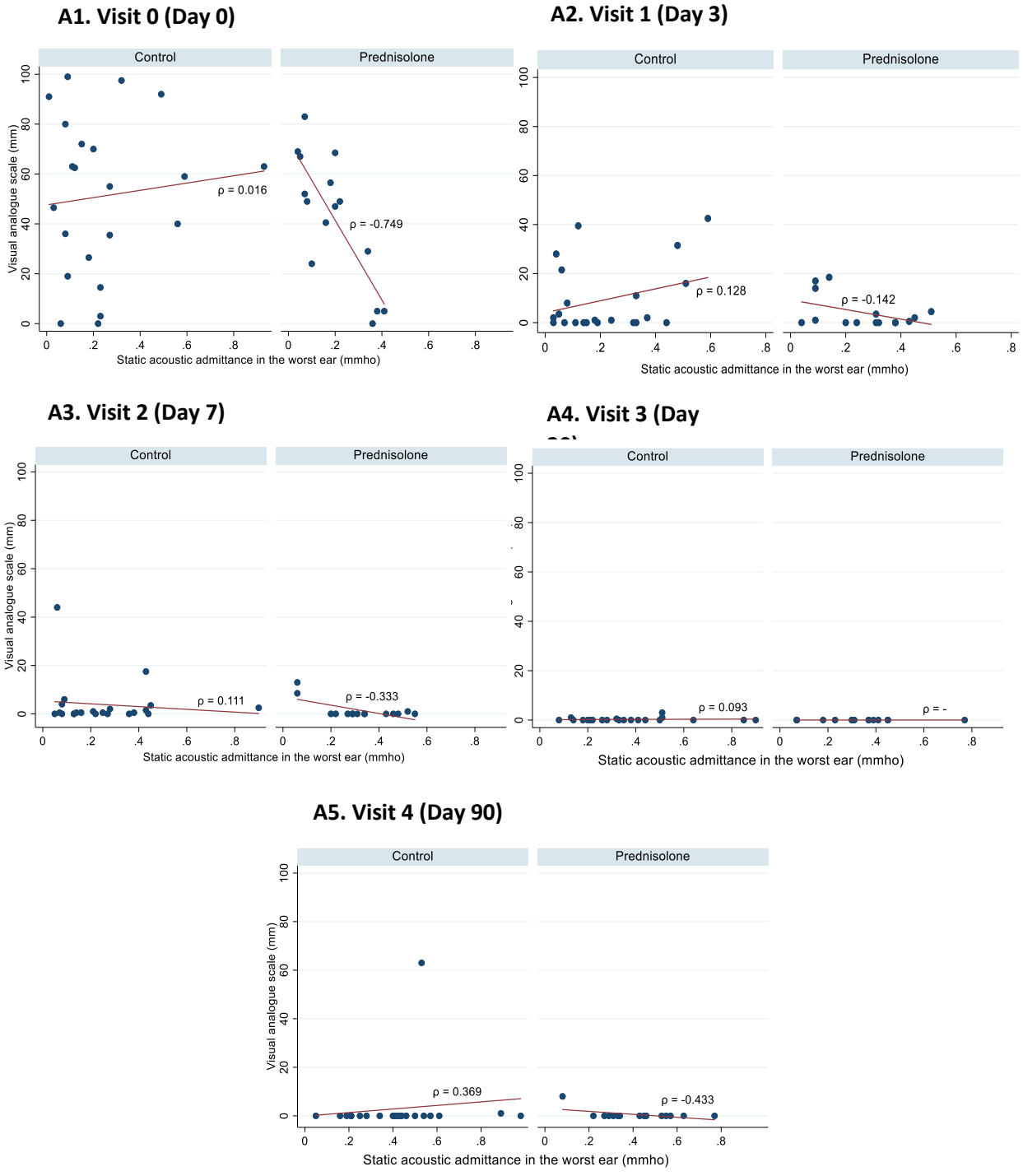
20. Marom T, Marchisio P, Tamir SO, Torretta S, Gavriel H, Esposito S. Complementary and alternative medicine treatment options for otitis media. Medicine. 2016;95(6):e2695.
21. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, et al. A randomised, placebo-controlled trial of the effect of antihistamine of corticosteroid treatment in acute otitis media. J Pediatr. 2003;143:377-385.
22. Chen Y, Li K, Pu H, Wu T. Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2011; doi: 10.1002/14651858.CD007720.pub2.
23. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015; doi: 10.1002/14651858.CD004405.pub5.
24. Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. Cochrane Database Syst Rev. 2018; doi: 10.1002/14651858.CD012289.pub2.
25. Ruohola A, Heikkinen T, Jero J, Puhakka T, Juvén T, Närkiö-Mäkelä M, et al. Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes. J Pediatr. 1999;134:459-463.
26. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child 2016;0:1-6.
27. Ranakusuma WR, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, et al. Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study (OPAL study). Pilot and Feasibility Studies. 2018;4:146.
28. Francis NA, Cannings-John R, Waldron CA, Thomas-Jones E, Winfield T, Shepherd V, et al. Oral steroids for resolution of otitis media with effusion in children (OSTRICH): a double-blinded, placebo-controlled randomised trial. Lancet. 2018; 392: 557-568.
29. Nozza RJ, Bluestone CD, Kardatzke D, Bachman R. Identification of middle ear effusion by aural acoustic admittance and otoscopy. Ear Hear. 1994;15:310-323.
30. Zielhuis GA, Els W. Heuvelmans-Heinen EW, Rach GH, Van Den Broek P. (1989) Environmental Risk Factors for Otitis Media with Effusion in Preschool Children. Scandinavian Journal of Primary Health Care. 1989;7(1):33-38.
31. Green LA, Culpepper L, de Melker RA, Froom J, van Balen F, Grob P, et al. Tympanometry Interpretation by Primary Care Physicians. J Fam Pract. 2000 October;49(10):932-936.
32. Engel J, Anteunis L, Chenault M, Marres E. Otoscopic findings in relation to tympanometry during infancy. Eur Arch Otorhinolaryngol. 2000;257:366-371.
33. Onusko E. Tympanometry. American Family Physician. 2004;70(9):1713-1720.

34. Von Baeyer C. Children's self-report of pain intensity: what we know, where we are headed. Pain Res Manag. 2009;14(1):39-45.
35. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analogue pain score for children. Ann Emerg Med. 2001;37(1):28-31.
36. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain. 2003 Sep;4(7):407-414.
37. Shaikh N, Hoberman A, Paradise JL, et al. Responsiveness and construct validity of a symptom scale for acute otitis media. Pediatr Infect Dis J. 2009;28(1):9-12.
38. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, Gaboury I, Little P, Hoes AW. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368:1429-1435.
39. Pernica JM, Steenhoff AP, Mokomane M, Moorad B, Lechiile K, Smieja M, et al. Rapid enteric testing to permit targeted antimicrobial therapy, with and without Lactobacillus reuteri probiotics, for paediatric acute diarrhoeal disease in Botswana: A pilot, randomized, factorial, controlled trial. PLoS ONE. 2017;12(10):e0185177.
40. Ali S, Egunsola O, Babar ZUD, Hasan SS. Challenges of conducting clinical trials in Asia. Int J Clin Trials. 2018;5(4):194-199.
41. Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, et al. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. Trials. 2014;15:399.
42. Sanderson E, Smith GD, Bowden J, Munafò MR. Mendelian randomisation analysis of the effect of educational attainment and cognitive ability on smoking behavior. Nature Communications 2019; doi: 10.1038/s41467-019-10679-y.
43. Amani S, Yarmohammadi P. Study of Effect of Household Parental Smoking on Development of Acute Otitis Media in Children Under 12 Years. Glob J Health Sci. 2016 May;8(5):81-88.
44. Csákányi Z, 1, Antal Czinner A, John Spangler J, Todd Rogers T, Katona G. Relationship of environmental tobacco smoke to otitis media (OM) in children. Int J Pediatr Otorhinolaryngol. 2012 July ;76(7): 989-933.
45. Strachan DP, Cook DG. Parental smoking, middle ear disease and adenotonsillectomy in children. Thorax. 1998 Feb;53:50-56.
46. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res. 2011 May;45(5):626-629.

47. De Sutter AIM, van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane Database of Systematic Reviews. 2012; doi: 10.1002/14651858.CD004976.pub3.
48. Birnie KA, Hundert AS, Lalloo C, Nguyen C, Stinson JN. Recommendations for selection of self-report pain intensity measures in children and adolescents: a systematic review and quality assessment of measurement properties. Pain. 2019;160(1):5-18.
49. Castarlenas E, Jensen MP, von Baeyer CL, Miro J. Psychometric Properties of the Numerical Rating Scale to Assess Self-Reported Pain Intensity in Children and Adolescents A Systematic Review. Clin J Pain. 2017;33:376-383.
50. Tsze DS, Hirschfeld G, von Baeyer CL, Bulloch B, Dayan PS. Clinically significant differences in acute pain measured on self-report pain scales in children. Acad Emerg Med. 2015; 22(4):415-422.
51. Ruohola A, Laine MK, Tähtinen PA. Effect of antimicrobial treatment on the resolution of middle-ear effusion after acute otitis media. JPIDS. 2018:7:64-70.
52. Cutrera R, Baraldi E, Indinnimeo L, Del Giudice MM, Piacentini G, Scaglione F. Management of acute respiratory diseases in the pediatric population: the role of oral corticosteroids. Italian Journal of Pediatrics. 2017;43:31.
53. Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews. 2011; doi: 10.1002/14651858.CD003423.pub3.
54. Loughnan A, Deng C, Dominick F, Pencheva L, Campbell D. A single-centre, randomised controlled feasibility pilot trial comparing performance of direct laryngoscopy versus videolaryngoscopy for endotracheal intubation in surgical patients. Pilot and Feasibility Studies. 2019;5:50.
55. Carroll SL, Stacey D, McGillion M, Healey JS, Foster G, Hutchings S, et al. Evaluating the feasibility of conducting a trial using a patient decision aid in implantable cardioverter defibrillator candidates: a randomized controlled feasibility trial. Carroll et al. Pilot and Feasibility Studies. 2017;3:49.

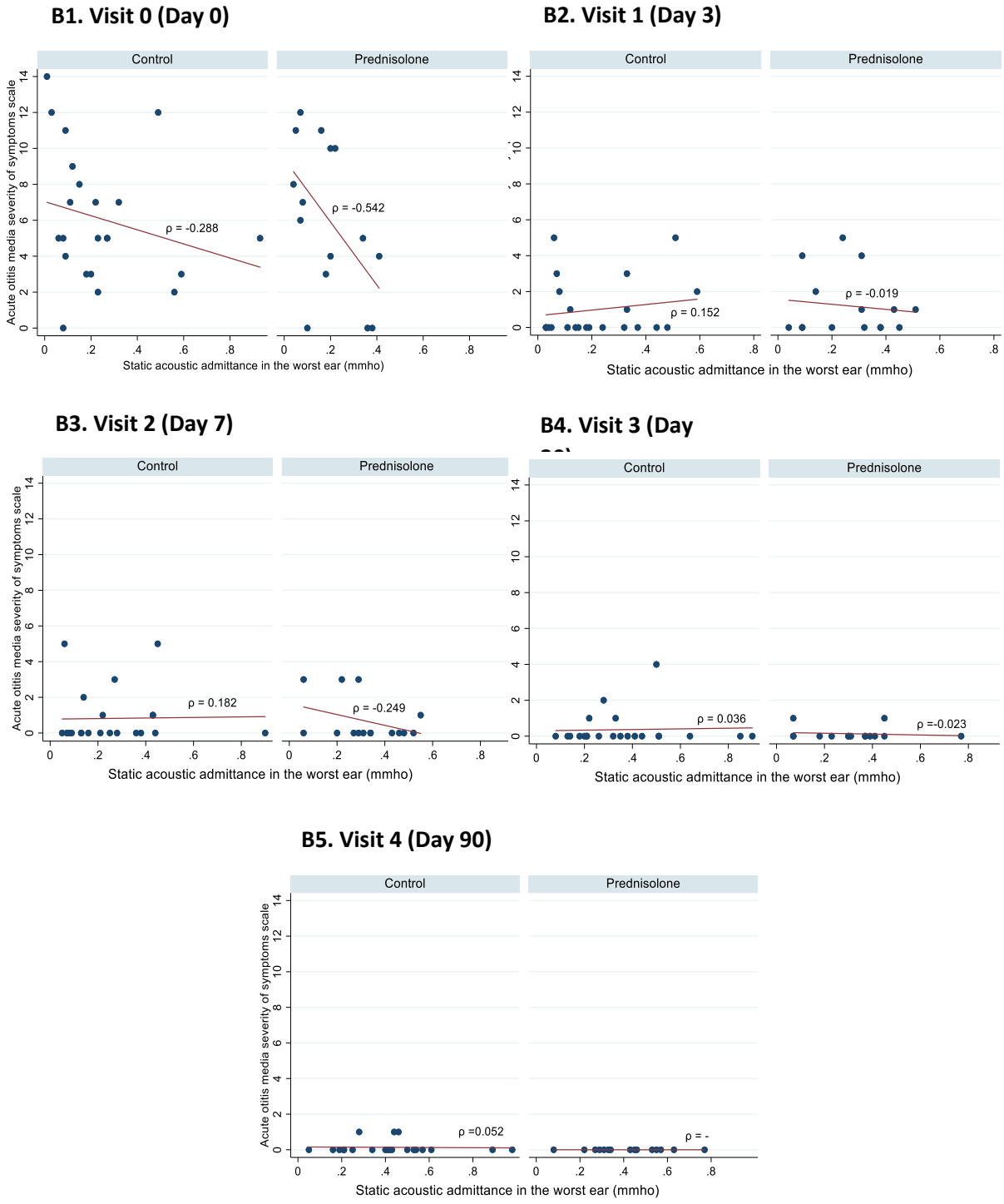
Appendix 1. Clinical outcomes of the pilot OPAL study.

Figure 1 Panel A. Correlation between pain measured using VAS and change in middle ear effusion*



ρ = Spearman's rank correlation coefficient

Figure 1 Panel B. Correlation between AOM-relevant symptoms measured using AOM-SOS and change in middle ear effusion.



ρ = Spearman's rank correlation coefficient

Table 1 Panel A – Clinical binary outcomes

Clinical outcomes*	Prednisolone (n=29)	Control (n=31)	Effect estimate (relative risk)	p value
Proportion of children with pain that has not reduced by 10 mm VAS at Day 3 (n; %)	3 (10)	5 (16)	1.07 (0.88, 1.30)	0.71
Proportion of children with pain represented by VAS ≥ 5mm (n: %)				
Day 0 (Visit 0)	27 (93)	27 (87)	1.07 (0.90, 1.26)	
Day 1	24 (83)	22 (71)	1.17 (0.88, 1.54)	
Day 3 (Visit 1)	6 (21)	14 (45)	0.46 (0.20, 1.03)	0.06
Day 5	3 (10)	8 (28)	0.37 (0.11, 1.27)	
Day 7 (Visit 2)	2 (7)	5 (17)	0.40 (0.08, 1.89)	
Day 14	1 (3)	2 (7)	0.50 (0.05, 5.21)	
Initiation of antibiotics or second-line antibiotics during Visit 1 to Visit 2 (n; %)	9 (31)	10 (32)	0.96 (0.46, 2.02)	> 0.999
Initiation of antibiotic for mild AOM in Visit 1 or Visit 2 (n; %)**	2 (33)	6 (86)	0.39 (0.12, 1.25)	0.11
Complications (n; %)	1 (3)†	0 (0)		0.49
Recurrence (n; %)				
Day 30 (Visit 3)	1 (3)	2 (7)	0.50 (0.05, 5.21)	> 0.999
Day 90 (Visit 4)	5 (17)	2 (7)	2.50 (0.53, 11.86)	0.42
Other descriptive outcomes				
Improvement of otoscopic findings compared to previous visit (n; %)				
Day 3 (Visit 1)	23 (79)	17 (55)		
Day 7 (Visit 2)	15 (52)	15 (52)		
Day 30 (Visit 3)	22 (76)	22 (76)		
Day 90 (Visit 4)	22 (76)	24 (83)		
Improvement of otoscopic findings compared to baseline (n; %)				
Day 3 (Visit 1)	23 (79)	17 (55)		
Day 7 (Visit 2)	21 (72)	21 (72)		
Day 30 (Visit 3)	24 (83)	25 (86)		
Day 90 (Visit 4)	26 (90)	27 (93)		
Tympanic membrane perforation (n; %)				
Day 0 (Visit 0)	11 (38)	8 (26)		
Day 3 (Visit 1)	4 (14)	6 (19)		
Day 7 (Visit 2)	3 (10)	3 (10)		
Day 30 (Visit 3)	1 (3)	2 (7)		
Day 90 (Visit 4)	1 (3)	1 (3)		
Treatment given by doctors in the study in two weeks following initial visit (n; %)				
Acetaminophen	9 (31)	17 (55)		
NSAIDs	5 (17)	8 (26)		
Decongestants and/or antihistamine	27 (93)	29 (93)		
Cough medicine	24 (83)	21 (68)		
Antibiotic ear drops	8 (28)	8 (26)		

Nasal topical decongestant	6 (21)	5 (16)
Nasal topical corticosteroid	8 (28)	3 (10)
Additional oral prednisolone	0 (0)	1 (3)
Vitamins or herbals	4 (14)	10 (32)
Ear diathermy	0 (0)	2 (6)
Inhalation	1 (3)	1 (3)
Others‡	4 (14)	7 (23)
Treatment given by other doctors or self-medication/over the counter in two weeks following initial visit (n; %)		
Antibiotics	1 (3)	1 (3)
Acetaminophen	2 (7)	1 (3)
NSAIDs	0 (0)	0 (0)
Decongestants and/or antihistamine	4 (14)	2 (6)
Cough medicine	5 (17)	4 (13)
Antibiotic ear drops	0 (0)	1 (3)
Nasal topical decongestant	0 (0)	0 (0)
Nasal topical corticosteroid	0 (0)	0 (0)
Additional oral prednisolone	2 (7)	0 (0)
Vitamins or herbals	3 (10)	2 (6)
Ear diathermy	0 (0)	0 (0)
Inhalation	0 (0)	0 (0)
Others‡	2 (7)	0 (0)
Additional visit required (n; %)	6 (21)	10 (32)

*Two missing data from control group after Day 3 made total number of control group 29; **There were 6 cases of mild AOM in the prednisolone group and 7 cases in the control group; †Tympanic membrane perforation at Day 30, which healed at Day 90; ‡Others (e.g. mefenamic acid, nasal wash).

Table 1 Panel B – Clinical continuous outcomes

Clinical outcome*	Prednisolone (n=29)	Control (n=31)	Unadjusted mean differences	p value	Adjusted mean difference**	p value
Pain measured by VAS (mm) mean (SD)†						
Day 0 (Visit 0)	48.9 ± 27.1	49.6 ± 31.1	-0.63 (-15.74, 14.48)	0.93		
Day 1	25.7 ± 20.7	23.5 ± 20.9	2.14 (-8.63, 12.91)	0.69	2.33 (-7.54, 12.19)	
Day 3 (Visit 1)	3.9 ± 5.6	11.3 ± 15.2	-7.37 (-13.36, -1.39)	0.017	-7.36 (-13.40, -1.33)	0.018
Day 5	4.2 ± 15.2	5.5 ± 12.7	-1.27 (-8.63, 6.08)	0.73	-1.20 (-8.38, 5.98)	
Day 7 (Visit 2)	1.1 ± 2.8	3.9 ± 9.3	-2.84 (-6.47, 0.78)	0.12	-2.84 (-6.51, 0.82)	
Day 14†	0.6 ± 2.8	0.8 ± 1.9	-0.21 (-1.45, 1.04)	0.74	-0.21 (-1.46, 1.05)	
Day 30 (Visit 3)	1.5 ± 6.8	0.2 ± 0.6	1.33 (-1.21, 3.87)	0.30	1.32 (-1.24, 3.89)	
Day 90 (Visit 4)	2.3 ± 10.3	2.2 ± 11.7	0.05 (-5.76, 5.86)	0.99	0.04 (-5.81, 5.89)	
Symptoms measured by AOM-SOS mean (SD)†						
Day 0 (Visit 0)	6.4 ± 3.8	6.1 ± 3.6	0.32 (-1.61, 2.24)	0.74		
Day 1	3.2 ± 3.0	3.1 ± 2.5	0.07 (-1.35, 1.50,)	0.92	-0.03 (-1.31, 1.25)	
Day 3 (Visit 1)	1.2 ± 1.9	0.9 ± 1.6	0.27 (-0.63, 1.17)	0.55	0.22 (-0.64, 1.09)	0.60
Day 5	1.1 ± 1.7	0.7 ± 1.2	0.38 (-0.39, 1.15)	0.33	0.38 (-0.40, 1.16)	
Day 7 (Visit 2)	0.5 ± 0.9	0.8 ± 1.5	-0.31 (-0.96, 0.34)	0.34	-0.31 (-0.97, 0.35)	
Day 14†	0.9 ± 2.3	0.2 ± 0.5	0.72 (-0.16, 1.61)	0.11	0.71 (-0.16, 1.57)	
Day 30 (Visit 3)	0.2 ± 0.6	0.5 ± 1.2	-0.27 (-0.79, 0.24)	0.29	1.34 (-1.22, 3.90)	
Day 90 (Visit 4)	0.1 ± 0.4	0.1 ± 0.3	0.03 (-0.17, 0.23)	0.73	0.11 (-5.70, 5.92)	
Time to pain resolution‡ (median days)	2	3	-1	0.71		

*Two missing data from control group after Day 3 made total number of control group 29; **Adjusting for the baseline and intervention allocation; †VAS (ranged 0 to 100 mm), higher score representing worse pain. AOM-SOS (ranged 0 to 14 points), higher score for worse symptom; ‡We analysed 55 out of 60 children (28 prednisolone and 27 control): 5 children not included were four controls (two left the study and two did not have pain resolution in two weeks) and one prednisolone did not have pain resolution in two weeks observation.

CHAPTER 5: ORAL PREDNISOLONE FOR ACUTE OTITIS MEDIA IN CHILDREN: A PROPOSED PRAGMATIC, PARALLEL, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY (OPAL STUDY) (STUDY 5)

Ranakusuma RW, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, Beller EM. Oral prednisolone for acute otitis media in children: a proposed pragmatic, parallel, randomised, double-blind, placebo-controlled study (OPAL study). *Pre-print version*.

5.1 SUMMARY

Our previous studies showed that it was feasible to conduct a large, pragmatic, randomised clinical trial to test the effectiveness of oral corticosteroids for children with AOM in Indonesia. The pilot study also indicated that oral corticosteroids may be beneficial in reducing pain intensity and improving the tympanometry curve, but may cause drowsiness.

These findings confirmed that it is important to conduct an adequately powered, large, parallel, pragmatic, multicentre, stratified, double-blind, randomised, placebo-controlled study to test both the benefits and harm of oral corticosteroids in children with AOM.

This chapter presents the protocol for the proposed main trial, incorporating the necessary alterations derived from the results of the pilot study. The following pages in this chapter are the protocol for the main study that has been submitted for publication as an appendix of the pilot study results paper and is under review.

Protocol of the main OPAL study:

Oral prednisolone for acute otitis media in children: a proposed pragmatic, parallel, randomised, double-blind, placebo-controlled study (OPAL study)

Ranakusuma RW[1,2], McCullough AR[1], Safitri ED[2], Pitoyo Y[2], Widyaningsih W[2], Del Mar CB1, Beller EM[1].

[1]Institute for Evidence-Based Healthcare, Bond University, Robina, Queensland, Australia.

[2]Clinical Epidemiology and Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

1. Executive Summary

Background: Acute otitis media (AOM) is an acute middle ear infection particularly found in children. Antibiotics are commonly prescribed, despite most cases being sufficiently managed by observation and adequate pain management. Due to weak effects and potential risks of antibiotic use, such as side effects and antibiotic resistance, an alternative non-antibiotic treatment for AOM is required. Corticosteroids could be a candidate for AOM, yet there is insufficient evidence on their efficacy. We have planned a high-quality clinical trial to test the effectiveness of oral corticosteroids in improving clinical outcomes including reducing middle ear effusion (MEE) in children with AOM. Our trial is justified by our pilot study showing that oral corticosteroids potentially reduce pain intensity at Day 3 and improve tympanometry results at Day 7, although the observed difference was small. This adequately powered clinical trial will allow us to definitively conclude whether corticosteroids are an effective treatment for AOM along with its effect size.

Methods: This multicentre, pragmatic, randomised, double-blind, placebo-controlled study will recruit 444 children aged 6 months to 12 years with onset of AOM within 48 hours. We will stratify children based on healthcare facility type and AOM severity. Children will be randomly allocated to receive either prednisolone or placebo plus observation in mild AOM and either prednisolone or placebo plus antibiotics in severe AOM. Our primary aim is to assess the effectiveness of oral corticosteroids in improving pain at three days after randomisation. Secondary aims are to assess: (1) the effectiveness of corticosteroids in improving pain at other time points, reducing pain intensity and overall AOM-relevant symptoms, reducing time to pain resolution, and the need for antibiotic initiation (mild AOM) or second-line antibiotics (severe AOM), AOM complications and recurrence; and (2) the adverse effects of corticosteroids.

Discussion: High rates of antibiotic use for AOM indicates the need for alternative treatments. Due to the inflammatory nature of AOM, corticosteroids may be a suitable treatment. If our study shows positive results with enough benefits and sufficient effect size outweighing harm, we can offer oral corticosteroids as one potential alternative treatment for AOM and thereby reduce antibiotic use. This study will contribute to adding to the range of AOM non-antibiotic treatment and updating current AOM management guidelines which do not make recommendations about oral corticosteroids for AOM.

Keywords: Otitis media, Acute disease, Glucocorticoids, Anti-bacterial agents, Clinical trial protocol.
Trial registration: Not yet.

2. Background

Acute otitis media (AOM) is an acute middle ear infection commonly found in children [1-3]. High rates of antibiotic prescribing are evident [4,5], although only one third of children with AOM, namely those who have severe cases, will likely benefit from antibiotics [4,6,7].

Due to the potential harm of antibiotic use and its weak benefits in improving clinical outcomes, alternative treatments for AOM, such as corticosteroids as anti-inflammatory agents, are needed. Due to the uncertain effects of corticosteroids for AOM [8,9], we plan to conduct a high-quality clinical trial to assess the effectiveness of corticosteroids for children with AOM. We recently tested the feasibility of this in a pilot, pragmatic, randomised, single-blind, controlled trial, which demonstrated it was feasible to conduct all planned procedures and measurement for a high-quality clinical trial. We found that oral prednisolone may potentially reduce pain intensity at Day 3. We also found drowsiness as the most common adverse event in children in the prednisolone group, with no other adverse events commonly attributed to short-course oral corticosteroids nor serious adverse effects found. Therefore, we will conduct a large, pragmatic, double-blind, randomised, placebo-controlled to test the effectiveness of corticosteroids, including benefits and harm, in children with AOM.

3. Methods/Design

3.1 Aim and objectives

We aim to assess the effectiveness of oral corticosteroid as a monotherapy for children with mild AOM and as an addition to antibiotics for severe AOM.

Our primary objective is to assess the effectiveness of corticosteroids in improving pain at three days after randomisation.

Our secondary objectives are to assess: (1) the effectiveness of corticosteroids in: (a) improving pain at other time points; (b) reducing pain intensity; (b) reducing overall AOM-relevant symptoms; (c) reducing duration to pain resolution; (d) reducing the need of antibiotic initiation for children with mild AOM or second-line antibiotics treatment for children with severe AOM after 48-hour observation; (e) reducing the risk of AOM complications; and (f) reducing the risk of AOM recurrence; and (2) the adverse effects of corticosteroids.

3.2 Design

We will conduct a large, parallel, pragmatic, multicentre, stratified, double-blind, randomised, placebo-controlled with an allocation ratio of 1:1, where children will be randomly allocated to either receive oral prednisolone or placebo.

3.3 Study setting

This multicentre study will be conducted at six primary care centres and two hospitals in Central and East Jakarta, Indonesia. We will include four healthcare centres which participated in our previous pilot study (two primary care centres and two hospitals). We will identify four other primary care centres based on an adequate number of paediatric AOM patient visits and the convenience of study monitoring.

We will include general practitioners (GPs) from the primary care centres and ear-nose-throat (ENT) specialists from the hospitals in the recruitment and assessment process of the study. We will also include nurses for study randomisation and pharmacists for study medication storage, preparation, and dispensing.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

We will include children aged six months to 12 years old with AOM, defined as current onset (within 48 hours) of AOM-relevant symptoms (e.g. earache, ear discharge, ear tugging/rubbing or irritability in non-verbal children). Otoscopic findings of acute inflammation (e.g. erythema) and middle ear effusion (e.g. bulged tympanic membrane, air-fluid level) will confirm the diagnosis. Due to potential obstacles in otoscopic assessment in children (e.g. uncooperative,

narrow ear canal, ear wax) and the pragmatic nature of this study in reflecting real practice in the management of AOM, we will include children with symptoms strongly indicating AOM whose diagnosis cannot be confirmed using an otoscope, and diagnose these children with suspected AOM.

3.4.2 Exclusion criteria

We will exclude children who (1) have major and severe medical conditions (e.g. heart diseases, kidney failure, tuberculosis), (2) are immunocompromised (e.g. HIV infection, under cancer treatment), (3) have congenital malformations and/or syndromes (e.g. cleft palate, Down syndrome), (4) have high risk of strongyloidiasis infections, (5) have ear ventilation tube(s), (6) have been exposed to persons with varicella (chicken pox) or active Zoster infection in the past three weeks without prior varicella immunisation or infection, (7) have taken systemic (oral, injection) or topical steroids in the preceding four weeks, (8) have taken antibiotics in the preceding two weeks, and (9) are hypersensitive to prednisolone or prednisone, or other corticosteroids.

3.5 Interventions

3.5.1 Prednisolone

Prednisolone tablets (Lupred®5) will be given as a single daily dose of 1–2 mg/kg of body weight for five days. A wide therapeutic dose window of prednisolone allows the simplification of randomisation and dispensing as follows: 10 mg/day for children aged six months to up to two years; 20 mg/day for children aged two up to six years; and 30 mg/day for children aged six to 12 years [10]. We strongly recommend children take prednisolone as a whole (single dose) in the morning (6 to 8 am) to minimise the risk of hypothalamic–pituitary–adrenal (HPA) axis suppression and for the convenience of both the patients and their parents or care givers. We will provide a liquid sweetener to be added to the study medication to make it more palatable for the children. The parents or care givers will be asked to give the prednisolone with food or milk to decrease the risk of gastrointestinal disturbance.

Children with mild AOM who are randomly allocated to the intervention arm will receive prednisolone plus expectant observation, whilst those with severe AOM will receive prednisolone plus antibiotics.

3.5.2 Placebo

Children in the control group will receive a 5-day course of matched placebo which has similar form, colour, and taste to prednisolone.

Children with mild AOM who are randomly allocated to the control arm will receive placebo plus expectant observation, whilst those with severe AOM will receive placebo plus antibiotics.

3.6 Criteria for study drug discontinuation or modification

If a child vomits less than 30 minutes after taking a dose of study medication, parents will be instructed to give another dose and report to the research team for an additional dose for completing a 5-day course of study medication. However, if a child vomits after 30 minutes, parents should not give another dose until the next dose on the next morning. If a child keeps vomiting or experiencing other unfavourable effects (e.g. nausea, diarrhea) after receiving the study medication, parents should contact the research team. If the parents forget to give study medication, they can give the missed dose as soon as they remember on the same day. Any modification of taking study medication, such as above, should be recorded in the symptom diary.

If there are any adverse events and adverse drug reactions where the research team assesses discontinuation of study medication is required, the treatment will be discontinued; however, follow-up will continue, where possible.

3.7 Strategies to improve adherence to the intervention protocol

We will remind parents to complete a symptom diary and give the study medication to their children every morning for five days by sending them text-message reminders every morning for two weeks. We have also added a note at the bottom of the questionnaire in the first booklet of the symptom diary to remind them to give the study medication every morning for five days. We will ensure that all parents have enough study medication to complete a 5-day course of intervention.

We will ask parents to keep the paper wrap packaging from the 5-day course of study medication. We will collect these paper wraps during their second visit at Day 7 to check the adherence of the study participants in taking study medication per protocol.

We will provide an information card for each patient at the baseline visit. This card will provide a summary of the study, including the intervention used in the study, and will state no additional oral corticosteroid should be prescribed during the study where possible. The parents should take and show the information card to any doctor consultations, to avoid additional oral corticosteroid intake. The parents should record all prescribed medications from these consultations or any over-the-counter medications in the symptom diary.

3.8 Concurrent treatment

Physicians may prescribe medications for symptoms (e.g. antipyretic, analgesic, decongestant, inhalation) according to their usual practice and record all medication prescribed in the outcome form, which is one of the case report forms (CRFs) developed for the study.

The physicians must not prescribe oral corticosteroids. The nurses and research assistant will cross-check all prescriptions before dispensing them to the parents, to ensure no oral corticosteroids are prescribed. If a child unintentionally receives any additional oral corticosteroids, we will not exclude the child from the study due to intention-to-treat analysis of the study. At the end of the study, we will identify any additional oral corticosteroids prescribed either from participating physicians or other physicians using the outcome form and symptom diary. All decisions on prescribing by physicians will be made prior to randomisation.

3.9 Outcomes

3.9.1 Primary outcome

For the primary objective of assessing the effectiveness of corticosteroids in improving pain, we will assess the proportion of children with ongoing pain represented by visual analogue scales (VAS) score of 5 mm or more [11] at Day 3 following the randomisation. We will assess this outcome using the VAS from the symptom diary.

3.9.2 Secondary outcomes

For the secondary objective of assessing the effectiveness of oral corticosteroids in improving pain at other time points, reducing pain intensity, overall AOM-relevant symptoms, and time to pain resolution, we will measure: (1) the proportion of children with ongoing pain (VAS score of $\geq$ 5 mm) using VAS in the symptom diary at 24 hours, Day 5, Day 7, and Day 14; (2) reduction of pain intensity using VAS in the symptom diary; (3) reduction of overall AOM-relevant symptoms using the overall score of acute otitis media severity of symptoms scale

(AOM-SOS); and (4) time duration to pain resolution using VAS in the symptom diary. The reduction of pain intensity and overall AOM-relevant symptom outcomes will be measured at 24 hours, Day 3, Day 5, Day 7, and Day 14. The time duration to pain resolution outcome will be measured during a 2-week observation period.

For the objective of reducing the need for antibiotic initiation for AOM, we will measure the proportion of children who require antibiotic initiation after 48-hour observation in children with mild AOM or second-line antibiotic treatment for children with severe AOM by two weeks after randomisation (Day 14).

For the objective of reducing the risk of AOM complications, we will measure the proportion of children who experience any complications of AOM, such as perforation of tympanic membrane or acute mastoiditis within two weeks following the baseline visit.

For the objective of reducing the risk of AOM recurrence, we will measure the proportion of children who experience at least one new episode of AOM within one and three months following the baseline visit.

For the objective of assessing the adverse effects of corticosteroids, we will measure the proportion of children who experience unfavourable side effects after taking the medication prescribed for the study within two weeks following the baseline visit.

3.10 Participant timeline

Table 1 illustrates the timeline for visits and follow-ups. Patients should visit the primary care centres or hospitals at Day 3 and Day 7 for re-assessment where physicians will identify the resolution of AOM symptoms (e.g. ear pain and other AOM-related symptoms) and clinical signs using an otoscope. During these visits, we will collect the first two booklets of the symptom diary. The first booklet records the symptoms, complications, side effects, other doctor consultations, and list of medications taken from baseline until Day 3, whilst the second booklet records similar outcomes from Day 4 to Day 7. At Day 3, the nurse will check the left-over study medication and ensure the study medication is available for a 5-day course of intervention. At Day 7, the nurses will collect and count the paper wraps and any left-over study medication. The third booklet of the symptom diary also records similar outcomes from Day 8 to Day 14 and will be collected during the home visit at Day 14. During the home visit, we will

not provide any prescriptions. Research assistants will contact all parents at Day 30 and Day 90 by phone to obtain information of AOM symptoms and recurrence of AOM.

Table 1. Follow-up timeline

	Study period						
	Enrolment Allocation	**Post-allocation**					**Close-out**
Timepoints	**0 (Day 0)**	**t1 (Day 3)**	**Intervention Ends* (Day 5)**	**t2 (Day 7)**	**Home visit (Day 14)**	**t3† (Day 30)**	**t4† (Day 90)**
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
INTERVENTIONS:							
[Intervention A] Prednisolone	—	—	—				
[Intervention B] Placebo	—	—	—				
ASSESSMENTS:							
General examination	X	X		X			
Pain severity using VAS	X	X	X	X	X		
Overall AOM-relevant symptoms using AOM-SOS	X	X	X	X	X		
Otoscopic examination	X	X		X			
Requirement of 1st line or 2nd line antibiotic initiation		X	X	X	X		
Complications	X	X	X	X	X		
AOM recurrence						X	X
Adverse events		X	X	X	X		

*Data will be collected from the symptom diary; †The follow-up on these time-points will be conducted through phone-calls.

3.11 Sample size

Based on our initial size calculation, we needed to enrol 760 children with AOM [12]. We had assumed that 30% of participants would have severe AOM [7], however our pilot study

demonstrated that 78% of our total sample was in the severe group with the risk of ongoing pain (≥ 5 mm VAS) in the control group at Day 3 of 42%. Of the children with mild AOM, 57% in the control group had ongoing pain at Day 3. The average proportion of children in the mild and severe groups with ongoing pain at Day 3 was 45.2%. With our original assumption of 0.70 risk ratio with steroids [7], we will only need to study 201 experimental and 201 control subjects to be able to reject the null hypothesis with probability (power) 0.8 and type I error probability of 0.05. We will use an uncorrected chi-squared statistic to evaluate the null hypothesis of no difference between groups. The total sample size becomes 444 with a 10% allowance for dropouts.

The significant difference in the sample size estimation between our original sample size and the pilot study, which was conducted in an urban setting in a developing country, is mostly influenced by our original calculation that used effect assumptions originating from a meta-analysis of clinical trials conducted in developed countries. This indicates that the study sample size may change depending on the settings where the study will be conducted. Table 2 presents our sample size assumptions if study is conducted in three different settings.

Table 2. Sample size assumptions for a clinical trial of corticosteroids for AOM conducted in different settings.

Proportion of children	Original assumption [7]*	Middle scenario	Pilot observed result†
With severe AOM	35%	56%	78%
With severe AOM AND ongoing pain	57.5%	50%	42%
With mild AOM	65%	43%	22%
With mild AOM AND ongoing pain	36%	46%	57%
With severe and mild AOM AND ongoing pain	31.6%	38.4%	45.2%
Sample size calculation‡	760	570	444

*From a meta-analysis of studies conducted in developed countries; †Our pilot study was conducted in a developing country, urban setting; ‡The sample size includes a 10% allowance for dropouts.

3.12 Recruitment and stratification

Prior to the study, we will provide training and study procedure manuals for the participating healthcare personnel (i.e. GPs, ENT specialists, nurses, pharmacists) which describe all processes and procedures for recruitment, stratification, outcome measures, and randomisation, including data collection and recording using CRFs and the symptom diary. We will also detail the severity criteria for AOM and instructions for clinical assessment using an otoscope. We expect the participating healthcare personnel will be able to effectively and sufficiently conduct these study procedures and measures. We will allocate research assistants to assist the study recruitment and randomisation at study sites.

We will recruit and stratify children based on the eligibility and stratification criteria. Since we will involve both GPs and the ENT specialists at the primary care centres and hospitals, we will stratify children based on healthcare centre levels (primary care versus secondary/tertiary care centres) and AOM severity (mild versus severe AOM). Children will be stratified into the severe group if they have at least one of the following criteria: (1) moderate or severe symptoms of AOM, locally (e.g. moderate or severe ear pain, mastoiditis), and/or systemically (e.g. fever with temperature 39°C or higher, irritable, vomiting); (2) moderate or severe signs of middle ear inflammation (e.g. hyperaemic tympanic membrane) and effusion (e.g. bulging, bulla formation, yellowish purulent appearance of tympanic membrane); (3) aged younger than two years with bilateral AOM; or (4) tympanic membrane perforation (see Figure 1).

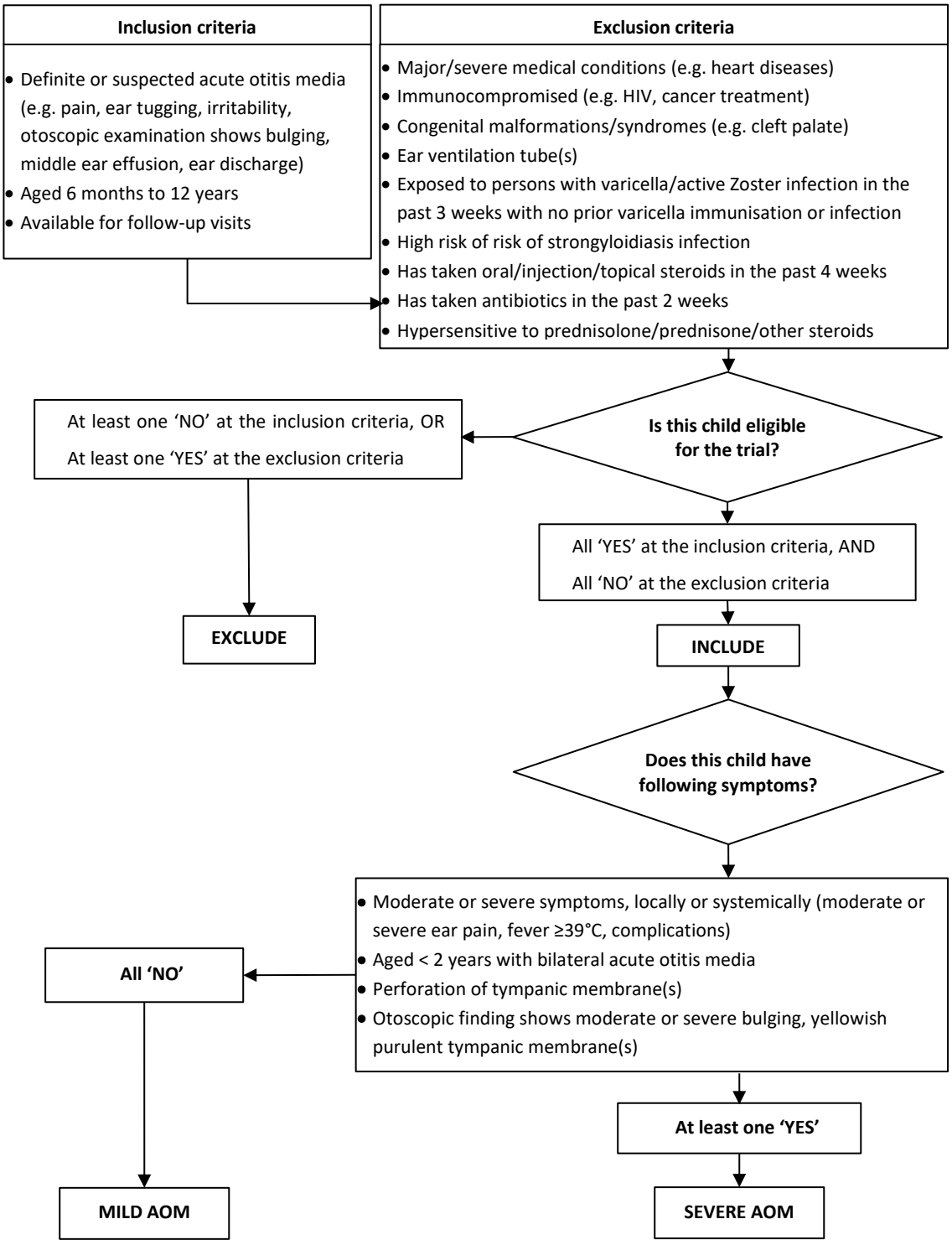


Figure 1. Eligibility and stratification diagram.

3.13 Randomisation and allocation concealment

All consenting eligible children and their parents will be enrolled and stratified based on healthcare service levels and AOM severity (see Figure 2). The physician will record the recruitment and the stratification in the eligibility form, whilst the nurse will later collect and record personal information of the study participants and their parents (e.g. date of birth, mobile phone numbers, home address) in the study registration form. Each study participant will be identified by a 3-digit study ID, which will be written on every CRF. The nurse will use the eligibility and study registration forms for randomisation purposes. We will provide two options to access the study randomisation: either the nurse can access MASCoT (an online randomisation generator developed by the Institute for Evidence-Based Healthcare (IEBH), Bond University, Queensland, Australia), or contact our 24-hour call centre, if using MASCoT is not possible. A successful randomisation will provide a 3-digit randomisation ID, which will be recorded in the randomisation form and study prescription. A permuted block randomisation sequence will be computer-generated by MASCoT, prior to study commencement. The allocation sequence will remain concealed throughout the study. No one but the statistician, who is blinded to study condition and concurrent medication, has access to MASCoT except for any emergency cases requiring unblinding. The children will then be randomly allocated to either prednisolone plus expectant observation, or placebo plus expectant observation alone in the mild group; and either prednisolone plus antibiotic, or placebo plus antibiotic in the severe group.

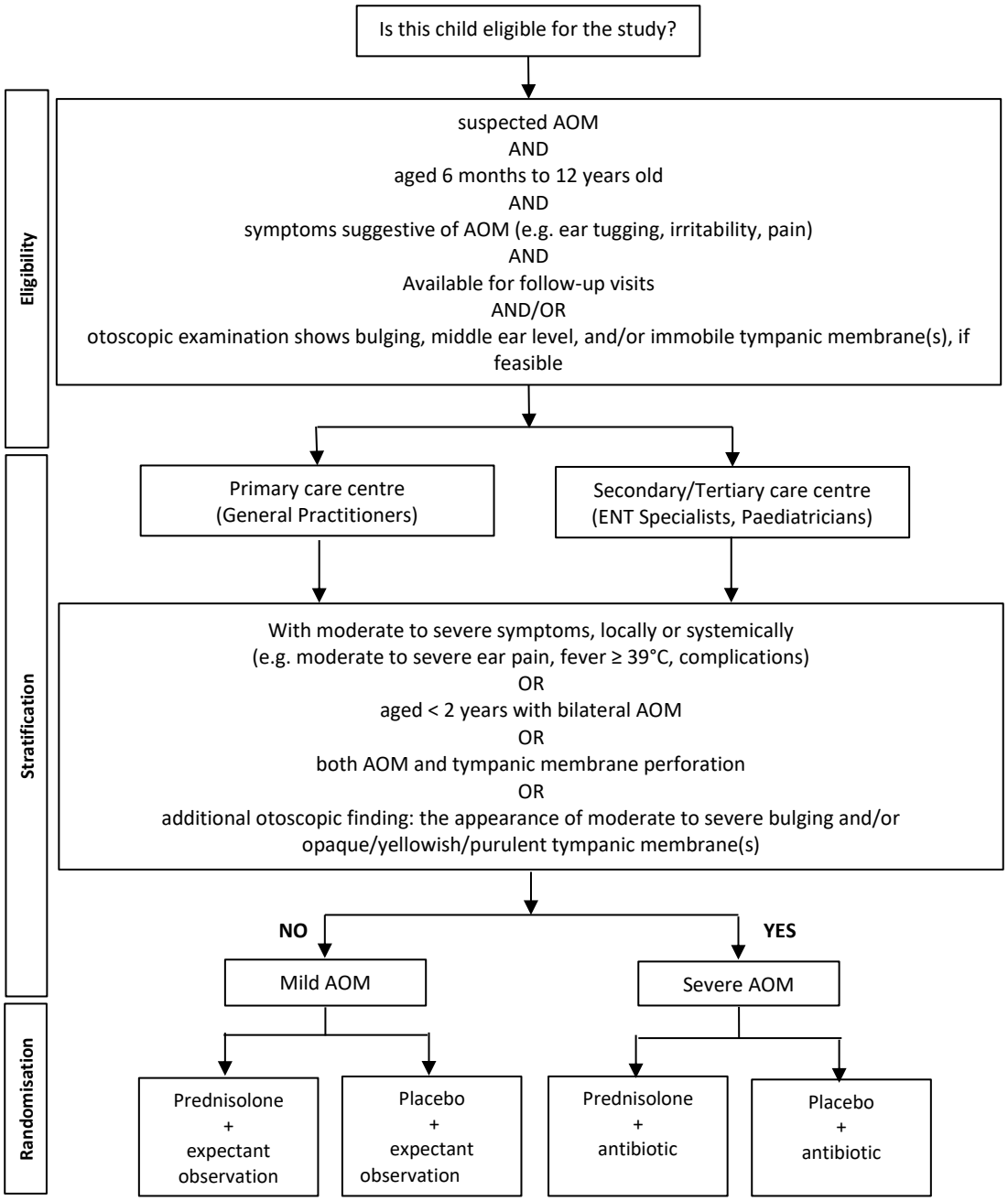


Figure 2. Flow chart of the stratification and randomization of the study

During the consultation, the physician will dispense two prescriptions to the nurse. The first prescription is for concurrent medications (e.g. antibiotics for severe AOM, analgesics, decongestants); whilst the second prescription is for study medication. The second prescription will provide clear information on the dose of study medication (based on the age), date of birth (to confirm the dose), and registration ID (for the allocation of the study medication). Randomisation ID will be added after the randomisation process by the study nurse.

Using the information in the prescription, the pharmacist will prepare the study medication, either the prednisolone or placebo, by crushing the tablets based on the prescribed dose and mixing them with sweeteners, then pack the mixed powder in five daily paper wraps. The pharmacist will then dispense the study medication along with instructions for the parents, and record the dispensing on the form provided by the study for this purpose. Batches of study medication will be dispatched to participating healthcare centres from a central pharmacy facility at the Clinical Research Supporting Unit, Faculty of Medicine Universitas Indonesia (CRSU FMUI).

3.14 Blinding

The physicians, nurses, pharmacists, research assistants, and both study participants and their parents will be blinded to the intervention allocation throughout the study. Emergency unblinding can occur if there are serious adverse events (SAEs). The unblinding result will be limited only to the treating physician, the parent/caregiver of the study participant who is experiencing the SAE, the study statistician, and the principal investigator.

3.15 Data collection methods

We will collect all data and outcome using CRFs (i.e. consent form, eligibility form, outcomes form, randomisation form, serious adverse effects form) and a symptom diary.

To assess the proportion of children with ongoing pain (VAS score of ≥ 5 mm) and reduction of pain intensity at various timepoints, we will use the VAS score in the symptom diary which will be completed by the parents or older capable study participants. The VAS is a well-established and validated scale for pain assessment and commonly used for research [13]. This 100-mm horizontal pain scale has a ‘no pain’ anchor at the left and a ‘the most severe pain’ at the right endpoint. We will measure the distance between the left endpoint to a vertical line crossing the horizontal scale which represents the intensity of the pain. This vertical line will be marked by the parents or study participants aged eight years or older who are capable of self-pain measurement [14]. We will identify whether the reduction of pain intensity is clinically meaningful by using VAS score of 10 mm as a minimum clinically important difference between groups [15,16].

To assess the reduction of overall AOM-relevant symptoms, we will use the AOM-SOS that will be completed by the parents in the symptom diary. We will use AOM–SOS to identify

other symptoms that are commonly found in young children with AOM [17]. The scale consists of three possible intensities of symptoms, which are 'no' (0 point), 'a little' (1 point), and 'a lot' (2 points), Table 2. The minimum clinically important difference between groups for total AOM-SOS points is 4.2 points [17]. Prior to the pilot study, we translated the AOM-SOS to the Indonesian language [12].

Table 3. Acute otitis media severity of symptoms scale (AOM-SOS) [17]

We are interested in finding out how your child has been doing. For each question, please place a check mark in the box corresponding to your child's symptoms. Please answer all questions.	**No**	**A little**	**A lot**
Over the past 12 hours, has your child been tugging, rubbing, or holding the ear(s) more than usual?	☐	☐	☐
Over the past 12 hours, has your child been crying more than usual?	☐	☐	☐
Over the past 12 hours, has your child been more irritable or fussy than usual?	☐	☐	☐
Over the past 12 hours, has your child been having more difficulty sleeping than usual?	☐	☐	☐
Over the past 12 hours, has your child been less playful or active than usual?	☐	☐	☐
Over the past 12 hours, has your child been eating less than usual?	☐	☐	☐
Over the past 12 hours, has your child been having fever or feeling warm to touch?	☐	☐	☐

To assess the need for antibiotics, we will use the outcome form completed by participating clinicians and the symptom diary completed by the parents to identify any antibiotic prescribing from other physicians for AOM or other health issues. We will identify any antibiotic initiation for children in the mild group or second line antibiotics for children in the severe group during the first two weeks of the study.

To assess complications and adverse events, we will also use the outcome form and the symptom diary. In terms of adverse events, we will provide several common side effects related

to corticosteroid use in the symptom diary. We will also ask parents to record any other side effects that are not listed in the symptom diary.

To assess AOM recurrence, we will interview the parents by phone at Day 30 and Day 90. We will identify any new episode of AOM and record this in the outcome form.

To promote study retention and complete follow-up, we will send a daily text message reminder to the parents during the first two weeks. This message will remind the parents to give the study medication to their children for five days and to complete the symptom diary for two weeks. We will remind the parents to take their children for the follow-up visits at Day 3 and Day 7. We will confirm their visit one to three days prior to the scheduled time, which allows us to organise another time or home visit if they are not able to come. If the study participants are not able to come at the scheduled follow-up time, we will encourage them to come up to maximum of three days over the scheduled time. We will provide an incentive in the form of reimbursement for their transportation to and from the primary care centres/hospitals and a small souvenir for study participants. We will advise the parents to take their children to the primary care centres/hospitals if there are any concerning conditions or no improvement. We will record any cases of discontinuation or deviation from study protocol in CRFs and continually follow these study participants per protocol where possible.

3.16 Data management

We will consistently conduct cross-checks during and after data entry to maintain the integrity and completion of data, particularly for missing data or errors. We will document all data entry and modifications in the database which will be available for viewing. Any modifications to the study data will be completed with the name, date, and signature of the person who is responsible for data modification. For missing or erroneous data, we will confirm the study data in the database using the original CRFs or by sending queries to the originating site. The central data coordinator will check the validity and completeness of study data on a regular basis. All data in the central database will be protected with a regular complete back up system.

3.17 Statistical methods

For dichotomous outcomes (i.e. the proportion of children with ongoing pain at various time points, who require antibiotic initiation in mild group or second-line antibiotics treatment for children with severe group after 48-hour observation, with complications related to AOM, and

with AOM recurrence), we will conduct a chi-squared test to determine the differences between two groups in outcome, expressed as relative risk (RR) with 95% confidence intervals (CI) and p values. A secondary analysis will use multiple logistic regression to adjust the primary outcome for allergy or atopy, siblings, first episode of AOM before the age of 12 months, passive smoking, breastfeeding duration less than three months, low parental education level, and day care attendance.

We will report the proportion of children with adverse events and children who are adherent to the study and study medication in percentages.

For continuous outcomes of reduction of pain intensity measured using VAS and overall AOM-relevant symptoms measured using AOM-SOS, we will conduct independent t-tests to determine the differences between two groups in mean score, expressed as mean difference (MD) with 95% CIs and p values. We will also conduct multiple linear regression, adjusting for similar factors as the multiple logistic regression above (equivalent to ANCOVA). For outcome of time duration to pain resolution, we will use a log rank test to compare the time to pain resolution between the two groups. We will use Kaplan-Meier survival plots to show the proportion of children who experienced the outcomes at each time point. We will use STATA 15.1 software for statistical analysis.

We plan to analyse by intention-to-treat; however, if there is loss to follow-up, we will use an available case analysis. We will still record data on study participants who stop study medication, where possible, and will include them in the analysis where outcome data are available.

4. Data monitoring

An independent person from Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit, Dr. Cipto Mangunkusumo Hospital (CMH) – Faculty of Medicine Universitas Indonesia (FMUI) will perform data monitoring periodically. She will review the process of patient recruitment, data entry, and study data storage in the central database, and report the results to the steering committee and sponsor as to whether the research has been conducted appropriately based on the approved research protocol.

We will perform an interim-analysis when 50% of patients have been randomised and have completed the 3-month follow-up. The interim analysis will be conducted by independent

statistician from CRSU FMUI, who will be blinded to the treatment allocation and will report to a data and safety monitoring committee (DSMC) in CRSU FMUI. The DSMC will receive access to unblinded data of the trial if requested and will make recommendations to the steering committee without revealing specific details of the results unless there is a strong recommendation to cease the study. The decision on the continuation of the trial will be decided by the steering committee based on the recommendation from the DSMC.

5. Harm

We define adverse events (AEs) as 'any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with study medication', whereas adverse effects or adverse drug reactions (ADRs) are defined as 'all noxious and unintended responses to a study medication related to any dose' [12]. Data collection of any AEs and ADRs commences after we obtain consent from the parents and enrol the eligible children into the study. We will record all AEs or/and ADRs following the enrolment during the study in the outcome form and serious adverse effects form. We will also use an adverse event assessment form which will be completed by an expert team established for this purpose. The expert team includes paediatricians and ENT specialists who have experience in conducting a clinical trial and are competent in the clinical fields of paediatric inflammatory disorders.

We define serious adverse events as 'any untoward medical occurrence at any dose that may result in-patient and/or prolonged hospitalisation, persistent or significant disability, medically important events, life-threatening events, and death' [12]. A detailed information of the management of serious adverse events in the study can be retrieved from our pilot study protocol [12].

6. Auditing

We will establish an independent audit committee from the CRSU FMUI and CEEBM Unit CMH-FMUI. This independent committee will conduct monitoring of source paper and electronic documents in the electronic database, monitor the conduct of trial in multicentre sites, interview the investigators and coordinators, and check the storage, distribution, and the use of study medication. Before the commencement of the study, the committee will ensure that the research staff are competent in data entry and in using the electronic database. These processes will be conducted according to the protocol and International Conference Harmonization –

Good Clinical Practice (ICH-GCP) standards. The data monitoring is scheduled to be conducted every six months from the research head office (CEEBM Unit CMH-FMUI) and trial sites.

7. Ethics and dissemination

Research ethics approval

This study will be conducted according to the Declaration of Helsinki and ICH-GCP guidelines. We will obtain research ethics approval from the Bond University's Human Research Ethics Committee (BUHREC) Australia and the Ethics Committee FMUI Indonesia. We will also seek permits to conduct clinical research from the One Stop Integrated Service Agency, Province of DKI Jakarta and from each study site.

Protocol amendments

Any modifications to the protocol which may impact on the trial process (e.g. the modification of study objectives, study design or/and procedures, study population, sample sizes), potential benefits and safety of the study participants will require a formal amendment to the protocol. This amendment will be sent to and approved by the funding body and the Ethics committee prior to its implementation. Notification will also be sent to the health authorities in accordance with local regulations. Minor modifications that may not impact on the trial process will also be notified and approved by the funding body and will be notified to The Ethics Committee.

Consent or assent

Before obtaining consent for their participation in the study, we will provide structured and detailed study information, such as the justification for the study, all study procedures, and expected commitment of the parents/caregivers during the study (e.g. give the study medication, complete the symptom diary, and come to follow-up visits per protocol), as well as potential side effects from the study medication. We will obtain the consent of study participation from children aged 12 years and over. The person who delivers the consent interview will also provide their signature on the consent form, stating that they have provided information and opportunity for potential participants to understand and raise relevant questions about the study. We will ensure the consent process is free of coercion, and that parents understand their right to withdraw from the study at any time without any consequences on healthcare services, as participation is voluntary.

Confidentiality

The original CRFs and other study information will be stored in a secure locked file cabinet at each participating site, with copies at the central research office. All study information stored in the study database will be secured with password-protected systems under limited access. We will use a 3-digit study ID as an identifier for CRFs and other forms related to the study. The study data storage will separate forms containing names (i.e. consent form, study registration form) from CRFs and other study forms. All counselling sessions will be conducted in private rooms. We will ask all participating healthcare personnel to maintain the confidentiality of study participants.

Data on every participant will be kept confidentially and will not be distributed externally without the written permission of the participant, except if it is required for trial monitoring by national regulatory authorities related to medical and research safety.

8. Access to data

The principal investigator (RR) will be given access to the cleaned data sets. RR will also have direct access to each site's data sets on request. Project data sets will be secured using passwords. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information. We will make our cleaned study data publicly available in the Bond University research repository (https://research.bond.edu.au/) after the completion of the study and the publication of the study results.

9. Ancillary and post-trial care

Any complications of AOM and potential adverse effects from the study will be closely monitored using the symptom diary. In case there is an emergency or worsening condition that requires comprehensive assessment and management, we will provide a 24-hour call centre and list of phone numbers and addresses of healthcare providers. We will be responsible for the treatment of any adverse effects that occur from the study medication during the study. The compensation will include costs such as consultation visits, additional examinations, and treatment (e.g. medicine, hospitalisation cost). Due to other potential concurrent treatments within the study, there will be robust review and analysis to ascertain the cause of adverse events. Information on management of adverse effects will be provided by physicians during the consent approval process before entering the study. We will also include this information

in the patient symptom diary. We will provide contact details of the 24-hour call centre and a list of recommended healthcare providers on the follow-up card.

10. Dissemination policy

We will report the study results in a medical journal and by presentations at conferences or other medical meetings. All investigators will review the manuscript and provide their consent for their acknowledgment and contribution before submission.

References

1. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. Clinical practice guideline: the diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964–e99.
2. Liese JG, Silfverdal SA, Giaquinto C, Carmona A, Larcombe JH, Garcia-Sicilia J, et al. Incidence and clinical presentation of acute otitis media in children aged <6 years in European medical practices. Epidemiol Infect. 2014;142:1778–88.
3. South Australian Child Health Clinical Network. Australian Policy Clinical Guideline South Australian Paediatric Practice Guidelines: Acute Otitis Media in Children. https://www.sahealth.sa.gov.au/wps/wcm/connect/a8910c004329b4dc81b8ed8bf287c74e/Acute+Otitis+Media+in+children_May2014.pdf?MOD=AJPERES&CACHEID=a8910c004329b4dc81b8ed8bf287c74e. Published February 2014. Accessed February 22, 2016.
4. McCullough AR, Pollack AJ, Hansen MP, Glasziou PP, Looke DFM, Britt HC, et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. Med J Aust. 2017;207(2):65–9.
5. Henderson J, Valenti L, Miller GC. General practice antibiotic prescribing for management of otitis media in children. Aust Fam Physician. 2016;45(6):363-5.
6. Le Saux N, Robinson JL, Canadian Paediatric Society Infectious Diseases and Immunization Committee. Management of acute otitis media in children six months of age and older. Paediatr Child Health. 2016;21(1):39-44.
7. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368:1429-1435.
8. Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. Cochrane Database Syst Rev. 2018;3:CD012289. https://doi.org/10.1002/14651858.CD012289.pub2.

9. Ruohola A, Heikkinen T, Jero J, Puhakka T, Juvén T, Närkiö-Mäkelä M, et al. Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes. J Pediatr. 1999;134:459–63.
10. Francis NA, Cannings-John R, Waldron CA, Thomas-Jones E, Winfield T, Shepherd V, et al. Oral steroids for resolution of otitis media with effusion in children (OSTRICH): a double-blinded, placebo-controlled randomised trial. Lancet. 2018;392:557-68.
11. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain. 2003 Sep;4(7):407-14
12. Ranakusuma WR, McCullough AR, Safitri ED, Pitoyo Y, Widyaningsih, Del Mar CB, et al. Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study (OPAL study). Pilot and Feasibility Studies. 2018;4:146. https://doi.org/10.1186/s40814-018-0337-x.
13. Huguet A, Stinson JN, McGrath PJ. Measurement of self-reported pain intensity in children and adolescents. J Psychosom Res. 2010;68:329–36.
14. Cohen LL, Lemanek K, Blount RL, et al. Evidence-based assessment of paediatric pain. J Pediatr Psychol. 2008;33(9):939–56.
15. Von Baeyer C. Children's self-report of pain intensity: what we know, where we are headed. Pain Res Manag. 2009;14(1):39–45.
16. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analogue pain score for children. Ann Emerg Med. 2001;37(1):28–31.
17. Shaikh N, Hoberman A, Paradise JL, et al. Responsiveness and construct validity of a symptom scale for acute otitis media. Pediatr Infect Dis J. 2009;28(1):9–12.

CHAPTER 6: CONCLUSION AND IMPLICATIONS

6.1 KEY RESULTS

Antibiotic resistance is identified as a global health threat [1]. This health problem is mostly driven by the wide use of antibiotics for common diseases such as acute respiratory infections (ARI) [2-4]. One ARI with a high rate of antibiotic prescribing, despite its self-limiting nature, is acute otitis media (AOM) [5,6]. Alternative treatments which can replace antibiotic use are required, particularly for mild cases of AOM.

Our research was conducted in Indonesia based on the candidate's clinical experience as a clinician who witnessed the overuse of antibiotic treatment and oral corticosteroids for AOM. Although the use of corticosteroids (anti-inflammatory agent), as an alternative treatment, makes biological sense (the basic pathophysiology of AOM is middle ear inflammation), there is no evidence confirming the efficacy of oral corticosteroids for AOM.

This thesis identified the available evidence on systemic corticosteroids as an alternative treatment for AOM in children, assessed, and addressed the existing research gap in this field.

Study 1 – Cochrane review of systemic corticosteroids for acute otitis media in children.

A Cochrane review of low to very low quality evidence (2 trials, n = 252) demonstrated that there is uncertainty around the effect of systemic corticosteroids in improving clinical symptoms of AOM (e.g., ear pain, bulging membrane inflammation, longer duration of antibiotic treatment), particularly at Day 5 (relative risk [*RR*] 1.06, 95% confidence interval [CI] 0.97 to 1.16) and Day 14 (*RR* 1.05, 95% CI 0.95 to 1.17).

Strengths

This review was the first systematic review on oral corticosteroids for children with AOM that used a robust, systematic, and transparent process in methods and reporting. The uncertain result of this review reflected insufficient evidence about the efficacy of corticosteroids for AOM.

Limitations

We found only two small clinical trials with low to very low quality of evidence testing the efficacy of corticosteroids for children with AOM [7,8]. All children in both trials received systemic antibiotics, indicating the two trials used systemic corticosteroids as an addition to

antibiotics for children with severe AOM. Therefore, we were unable to assess the effects of systemic corticosteroids as a monotherapy for mild AOM where antibiotic is not indicated. None of the trials specifically assessed ear pain as one of the outcomes, which limited our ability to identify the effects of systemic corticosteroids for the resolution of ear pain. We also could not identify adverse events caused by systematic corticosteroids due to incomplete outcome reporting.

There was insufficient additional data provided by the authors of the included studies in the review. We contacted the authors, but they only provided us additional information regarding the randomisation, allocation concealment, and the blinding process of the clinicians and outcome assessors. They were unable to provide: (1) additional information on the proportion of children who had clinical failure/improvement from each group at each visit; (2) clinical information on children who did not complete the study (drop-out, loss of follow-up); (3) details of tympanometry results; and (4) adverse events in each group.

Our study demonstrated that there was insufficient evidence identifying the effect of corticosteroids for AOM, indicating more studies are needed in this field. Therefore, we planned to conduct a large high-quality clinical trial to assess the effectiveness of systemic corticosteroids for AOM in children.

Study 2 – Current management of children with acute otitis media: a feasibility survey for a pragmatic study in Jakarta, Depok, and Bekasi.

Insufficient evidence on systemic corticosteroids for AOM has confirmed the necessity for a high-quality clinical trial to assess the effectiveness of systemic corticosteroids for AOM in children. We planned to conduct a high-quality clinical trial to resolve this gap. As part of our plan to conduct a large, pragmatic randomised controlled trial (RCT) of systemic corticosteroids for AOM in children in Indonesia, we conducted a feasibility study surveying the current practice of Indonesian physicians in the management of AOM. Clinical scenarios in our feasibility survey showed that most Ear-Nose-Throat (ENT) specialists would prescribe antibiotics for children with mild, as well as recurrent AOM, whilst paediatricians were more likely to choose expectant observation by withholding antibiotic initiation. This study also demonstrated there were adequate numbers of: (1) AOM paediatric patients; (2) physicians who

would use oral corticosteroids; and (3) physicians who were willing to participate in our planned large RCT.

Strengths

This was the first survey study identifying the current management of AOM in children in Indonesia. This was a valuable contribution since physicians in Indonesia use two conflicting practice guidelines for AOM [9,10]. We also had the opportunity to re-introduce principles for the management of AOM adopted from international practice guidelines to Indonesian physicians, particularly in terms of antibiotic use, during dissemination of our survey at several workshops and conferences.

Limitations

We had a low response rate for this survey study that most likely was caused by voluntary participation and other potential factors (e.g., relevance of the topic to physicians, workload, insufficient access to obtain physicians' contact information) [11,12]. We were also unable to make the survey representative of all Indonesian physicians as we only included three cities in Indonesia due to the study purpose of a feasibility study for our future RCT. We planned to conduct our RCT in three adjacent cities, which were Jakarta, Depok, and Bekasi. We chose these cities for the convenience of conducting our RCT. Since all three cities are dominated by urban communities, we might not have captured any practice variation in rural communities, which was one of the limitations of this survey study. Collaboration with the Ministry of Health Republic of Indonesia, would have enabled us to identify the current management of AOM among physicians on a national scale. Another limitation of the study was the impact of study dissemination in workshops and conferences which may have influenced physicians in responding to the clinical scenarios in the questionnaire. The high antibiotic prescribing rate reported in our clinical scenarios may be an underestimation, as we had educated physicians about the limited efficacy and potential harms of antibiotic use in the management of AOM in children before distributing the survey.

In terms of the clarity of the questionnaire, we did not provide a clear description of corticosteroid treatment in our vignettes which could lead to different assumptions of the administration route of corticosteroids, whether it was oral or topical (nasal spray). This may not adequately reflect the purpose of the study in identifying the use of oral corticosteroids for AOM.

Findings from this study, despite its low response rate, supported our plan to conduct a large RCT of oral corticosteroids for children with AOM in Indonesia. To ensure the successful conduct of a large RCT, we conducted a pilot study to test our planned study procedures and measures.

Study 3 – Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, controlled study (OPAL study).

Our feasibility survey study confirmed it was feasible to conduct a clinical trial testing corticosteroids for children with AOM in Indonesia. Prior to the implementation of a large clinical trial, we piloted this study on a smaller scale. Within this study, we also conducted a mechanistic study (tympanometry study) to assess the mechanistic effect of corticosteroids, using tympanometry, in suppressing middle ear inflammation by reducing middle ear effusion (MEE).

A pilot pragmatic, randomised, open-label, controlled study

We conducted a pilot, randomised, open-label, controlled study in 62 children with AOM (mild AOM=15 and severe AOM=47) which demonstrated that all study procedures and measures were successfully conducted by all participating healthcare personnel, study participants, and their parents. It also showed that we needed to involve more primary care centres as recruiting sites, simplify study procedures, stratify children based on AOM severity and healthcare centre levels, and use placebo as a control. Our sample size re-calculation verified that we required a smaller number of study participants for our full RCT than originally thought. Our pilot study also showed that oral corticosteroids may potentially reduce pain intensity at Day 3.

Strengths

As well as refining the protocol for the main study, conducting the pilot enabled us to introduce the implementation of a clinical trial to healthcare personnel from different specialties and professional backgrounds who worked in several different healthcare institutions (primary care centres and hospitals). This experience will enhance their knowledge and skills to understand the principles of good clinical practice in clinical research and encourage their enthusiasm and willingness to conduct or to be involved in research in the future. Our study also introduced pain assessment tools and treatment options, such as expectant observation for mild AOM and antibiotic use for severe cases, as part of the management of AOM in children [13]. We also

explored the mechanism of oral corticosteroids in improving middle ear inflammation in AOM cases, which has not been sufficiently explored by existing studies.

Limitations

We found several limitations in this study: (1) the lengthy research administration process in the central and district-level government bodies; (2) a low recruitment rate due to lack of enthusiasm, time, and commitment among healthcare personnel; (3) the potential for performance bias due to the unavailability of placebo as a control; (4) technical obstacles in accessing the randomisation generator website (e.g., unstable internet connection, inadequate command of English); (5) unintentional additional oral corticosteroid prescriptions during the study; and (6) a limited generalizability of the results due to the majority of severe AOM cases in the pilot study. This meant our study result can only be generalised to countries which have similar practice to Indonesian clinicians (i.e., antibiotics and corticosteroids prescribing for AOM) and characteristics with our sample study, for which the majority were children with severe AOM. To resolve this issue in our future RCT, we plan to include more primary care centres to improve our recruitment, particularly of children with mild AOM.

These findings, despite the limitations, indicate that it was feasible and important to conduct a full-size pragmatic, randomised, double-blind, placebo-controlled study to assess the effects of oral corticosteroids for children with AOM. The results of the pilot study also indicated a potential trend of the beneficial effects of oral corticosteroids toward to the improvement of clinical outcomes of AOM, which requires to be confirmed in a large RCT.

A Mechanistic study using tympanometry (tympanometry study)

Within the pilot study, we also conducted a mechanistic study in 37 children (mild AOM=13 and severe AOM=24) by assessing middle ear effusion (MEE) using tympanometry. We found no difference in MEE change and in the proportion of children who had complete resolution of MEE between the prednisolone and control groups at Day 3, Day 7, Day 30, and Day 90. However, we found that oral corticosteroids may potentially improve tympanometry curve results at Day 7 (RR 1.76, 95% CI 1.04 to 2.97). We expected that there would be a strong correlation between the improvement of pain represented by lower scores on the VAS scale and AOM-SOS and resolution of MEE represented by higher values of static acoustic admittance. However, we found only a small correlation between the improvement of pain and other AOM-relevant symptoms and MEE at Day 3, Day 7, Day 30, and Day 90.

Strengths

By conducting this tympanometry study, we explored the mechanism of oral corticosteroids in improving middle ear inflammation in AOM cases, which has not been sufficiently explored by existing studies.

Limitations

We found tympanometry results were unreliable in demonstrating key findings in AOM cases with severe MEE. The tympanometry examination was costly and difficult to implement in children experiencing pain. It also required specific skills and facilities.

This mechanistic study showed that the tympanometry examination did not demonstrate a significant clinical benefit for the management of AOM. As only certain children may be at risk, this examination should be prioritized for children with risks of prolonged MEE (e.g., children with AOM aged < 2 years or, children with recurrent AOM), and not used for all AOM cases [13,14].

Study 4 – A protocol of a pragmatic, randomised, double-blind, placebo-controlled study of oral prednisolone for acute otitis media in children (OPAL study).

The previous three studies have led us to design our main study, which is a protocol for a pragmatic, multicentre, parallel, randomised, double-blind, placebo-controlled study of oral prednisolone for acute otitis media in children. The implementation of the pilot study demonstrated that it was feasible to successfully conduct all pre-specified procedures and outcome measures in the main study. There were several modifications needed to make all objectives of the main study achievable:

1. Study sites: more primary care centres (n = 6) and two private hospitals should be included
2. Research resources and logistics: more full-time research assistants should be employed.
3. CRFs should be modified and simplified.

Strengths

This study would be the first large, pragmatic, randomised double-blind, placebo-controlled trial testing corticosteroids as a monotherapy for mild AOM and as an addition to antibiotics

for severe AOM. If the study demonstrates positive results, it would then justify the use of oral corticosteroid as an effective treatment that can be used as a monotherapy in non-severe AOM, or as an addition to antibiotics in severe AOM to improve the resolution of ear pain and other clinical outcomes (e.g., other AOM-relevant symptoms, the need for initial antibiotics for non-severe AOM and the second-line antibiotics or a longer duration of antibiotic treatment for severe AOM, complications and recurrence of AOM).

6.2 IMPLICATIONS

6.2.1 IMPLICATION FOR PRACTICE

As our study was a pilot, it was not powered to demonstrate the effects of oral corticosteroids for children with AOM. However, it did not rule out an important benefit from corticosteroids. It demonstrated several potential harms (e.g., drowsiness) from the study which can be used by physicians to identify and sufficiently monitor side effects of a short-term use of oral corticosteroids in children. Other known side effects of corticosteroids (e.g., vomiting, diarrhoea) were not significantly higher in the corticosteroid group compared with control. One potential reason for physicians' reluctance to use corticosteroids for bacterial infections is due to the theoretical risk of immunosuppression with corticosteroids. Our pilot study demonstrated that there was no statistically significant difference between children in the corticosteroid and control groups in terms of experiencing worsening clinical episodes (e.g., requiring antibiotic initiation for mild AOM or second-line antibiotics for severe cases) or other outcomes (e.g., complications). Therefore, this study suggests that short-term corticosteroids are safe and not likely to cause worsening episodes of primary nor secondary infections of AOM.

The management of AOM based on the severity of AOM has been implemented in the pilot study. This has been recommended by the Indonesian practice guideline for ENT specialists [10], but not for GPs [9]. By implementing this in the primary care centres, we were able to disseminate a comprehensive management plan for AOM, which included the identification, diagnosis of AOM, as well as a rational and evidence-based treatment based on AOM severity. Although the national practice guideline for GPs recommends antibiotics for all AOM cases [9], our pilot study has shown that providing the treatment based on the AOM severity in primary care centres is a feasible and safe practice. Healthcare services provided by primary care centres is based on residential districts. This allows for sufficient follow-up visits during the 48-hour expectant observation period if required. Overall, the implementation of expectant

observation for mild AOM cases can reduce antibiotic prescribing in primary care centres, which would contribute in reducing the risk of antibiotic resistance.

As pain is the most common symptom found in AOM [15], pain assessment is an essential procedure in the management of AOM. This is not routinely practiced among Indonesian physicians. Therefore, identifying the baseline pain intensity and assessing its improvement during the follow-up visit will allow physicians to provide the best treatment for children with AOM.

Only half of surveyed physicians stated they would participate in our study. This demonstrated there was a lack of motivation of physicians to participate in research. In order to improve this, the Ministry of Health could support the implementation of clinical research by granting them rewards. One of the most valuable rewards is acknowledging physicians' contribution or collaboration to research by granting substantial additional credits for individuals and institutions. The individual credit can be added as extra points in the continuing professional development program of physicians and nurses, or as one requirement for their practice licence. The institutional credit could be acknowledged as part of the institutional accreditation program. This demonstrates that a particular healthcare institution has been involved in the implementation of research and the improvement of the quality of healthcare services, which could be an additional value for that institution. Direct involvement and contribution in the study will also contribute to the scientific publication rate of that particular institution.

6.2.2 IMPLICATIONS FOR RESEARCH

A large, high-quality clinical trial in assessing the effects of corticosteroids for children with AOM, particularly in uncomplicated and non-severe cases, is required. Our pilot study demonstrated that oral prednisolone may reduce pain intensity at Day 3. Although the difference did not quite reach the level deemed clinically important, a 10-mm score representing a clinically important difference was included in the confidence interval of the result from the pilot. This finding justified the importance of conducting a large and high-quality clinical trial to assess the effectiveness of oral corticosteroids for children with AOM.

Our tympanometry sub-study demonstrated a lack of benefit, and difficulties in conducting a tympanometry examination in paediatric AOM patients. However, it will be very useful to investigate specific baseline and clinical characteristics in our study which might contribute to predicting persisting MEE. In these cases, tympanometry would be beneficial to use for routine

assessment. Therefore, by recommending this only for children with high risk for persisting MEE and not in all AOM cases, this costly and difficult procedure will be more cost-effective [13,16].

We are aware that both Indonesian practice guidelines for AOM, particularly for ENT specialists, need to be updated since it was published in 2007 by the Otology Working Group of Indonesian Otorhinolaryngologist Head and Neck Surgeon Society [10]. We expect an updated guideline can provide more detailed information regarding the diagnosis and treatment for AOM, particularly the justification for antibiotic treatment, which was not provided in the current guideline. It would also provide information on other non-antibiotic treatments recommended or not recommended for AOM, along with the supporting evidence (e.g., acetaminophen, decongestants, corticosteroids). This updated guideline can then be implemented across specialties in Indonesia, including GPs and paediatricians. Following this, it is important to assess the adherence of physicians in sufficiently implementing this guideline in their daily practice. This will be a long-term plan for another potential research project assessing the implementation of the Indonesian practice guideline of AOM among physicians in Indonesia.

This pilot study showed that almost 80% of AOM cases were classified as severe, which is high compared with incidence rates found in studies conducted in developed countries. It would be very useful to have sufficient data about middle ear pathogens in AOM cases in Indonesia along with their antibiotic susceptibilities. This could be achieved with tympanocentesis or a less-invasive procedure, such as a nasal swab cross-sectional representative study of AOM cases. There are also underlying factors that may potentially influence antibiotic susceptibilities among Indonesian children: (1) lack of recommendation of the pneumococcus vaccination for Indonesian children; (2) geographical and demographical factors; and (3) practice of antibiotic prescribing in Indonesia. Identifying the causative AOM pathogens could contribute to improvements in the quality of prevention and comprehensive management of AOM, thereby improving the ear and hearing health in Indonesian children.

High antibiotic prescribing rates are also influenced by parents' expectations for antibiotic treatment [16]; there are many studies conducted mostly in developed countries identifying this issue. Our survey study identified current practice in the management of AOM among physicians. However, it will also be useful to identify the parents' and physicians' beliefs and perceptions about the use of antibiotics in the management of AOM in Indonesia. This

information can help physicians, researchers and health policy bodies to identify initial problems which influence the practice of antibiotic prescribing among Indonesian physicians and develop a strategy to limit this accordingly.

For the sustainability of the implementation of clinical trials in Indonesia, it would be very useful to survey healthcare practitioners who have been involved or participated in any clinical research regarding their experience, and their perception and expectation from conducting clinical research, including the limitations and obstacles that hold them back from being involved in research.

These research implications are important because of their potential contribution in tackling the antibiotic resistance problem in Indonesia. If these research projects are all implemented effectively, they can support reducing antibiotic use for AOM and eventually decrease the antibiotic resistance rate in Indonesia.

6.3 CONCLUSIONS

1. Our Cochrane review demonstrated there was insufficient evidence confirming efficacy of systemic corticosteroids for children with AOM, which indicated a requirement for high quality clinicals trials to be able to address this research gap.
2. Our feasibility survey study demonstrated:
    a. There was high rate of antibiotic prescribing for mild AOM among Indonesian physicians, particularly ENT specialists and GPs.
    b. Almost half of physicians would prescribe oral corticosteroids for children with AOM, although this is not recommended by existing AOM practice guidelines.
    c. It is feasible to conduct a clinical trial testing oral corticosteroids for children with AOM in Indonesia. A sufficient number of AOM paediatric patients and physicians would prescribe oral corticosteroids for AOM cases and were willing to participate in a clinical trial of oral corticosteroids for children with AOM.
3. Our pilot study demonstrated:
    a. It was feasible to apply all pre-specified procedures and outcome measures in the main study; however, several modifications are required (e.g., modification of recruitment and randomisation process, modification of case report forms).
    b. There was a lack of commitment to participate in the study among healthcare personnel due to high workload and time constraints.

c. Oral corticosteroids may potentially improve ear pain at Day 3. This result confirmed it is crucial to have an adequate sample size and high-quality clinical trial for a definitive conclusion on the effectiveness of oral corticosteroids for AOM.
d. Drowsiness is one of the unfavourable effects of corticosteroids in this study. However, there was no increased rate of other side effects compared with control.
e. Our under-powered tympanometry study indicated that oral corticosteroids may improve MEE at one week which was represented by the improvement of tympanometry curve type. However, due to lack of clear benefits and the difficulties in conducting this examination in paediatric AOM patients, we will not include tympanometry examination in the main study.
f. It is important to investigate predictor factors for persisting MEE in AOM cases to effectively restrict tympanometry examination for high risk patients as part of routine assessment in a comprehensive management of children with AOM. We have exploratory data from the pilot study to begin this process.

4. Conflicting Indonesian clinical practice guidelines may cause a discrepancy in the management of AOM among Indonesia physicians, particularly in terms of antibiotic treatment. This means it is crucial to update the current practice guidelines based on recent and high-quality evidence.

REFERENCES

1. About antimicrobial resistance. In: Antibiotic/antimicrobial resistance (AR/AMR). CDC Centers for Disease Control and Prevention https://www.cdc.gov/drugresistance/about.html. USA updated 10 September 2010.
2. Antibiotic resistance. World Health Organization. http://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance 5 February 2018.
3. The Centre for Clinical Practice National Institute for Health and Clinical Excellence (NICE). Respiratory tract infections – antibiotic prescribing: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. National Institute for Health and Clinical Excellence, London; July 2008. NICE Clinical Guideline 69.
4. Linder, JA. Antibiotics for treatment of acute respiratory tract infections: decreasing benefit, increasing risk, and the irrelevance of antimicrobial resistance. Clin Infect Dis. 2008;47:744-6.
5. McCullough AR, Pollack AJ, Hansen MP, Glasziou PP, Looke DFM, Britt HC, et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. The Medical Journal of Australia. 2017;207(2):65-9.
6. Henderson J, Valenti L, Miller GC. General practice antibiotic prescribing for management of otitis media in children. Aust Fam Physician. 2016;45(6):363-5.
7. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, et al. A randomised, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. J Pediatr. 2003;143:377-85.
8. McCormick DP, Saeed K, Uchida T, Baldwin CD, Deskin R, Lett-Brown MA, et al. Middle ear fluid histamine and leukotriene B4 in acute otitis media: effect of antihistamine or corticosteroid treatment. Int J Pediatr Otorhinolaryngol. 2003;67(3):221-30.
9. Ministry of Health Republic of Indonesia. Clinical practice guideline for clinicians in primary healthcare centres. Jakarta: Ministry of Health Republic of Indonesia; 2014. Regulatory No. 5 year 2014.
10. Otology Working Group of Indonesian Otorhinolaryngologist Head and Neck Surgeon Society. Guideline of ear, nose, and throat diseases in Indonesia [Guideline penyakit THT di Indonesia]. Jakarta: Indonesian Otorhinolaryngologist Head and Neck Surgeon Society; 2007.

11. Bonevski B, Magin P, Horton G, Foster M, Girgis A. Response rates in GP surveys. Trialling two recruitment strategies. Aust Fam Physician. 2011;40:427-30.
12. Pit SW, Vo T, Pyakurel S. The effectiveness of recruitment strategies on general practitioner's survey response rates – a systematic review. BMC Med Res Methodol. 2014;14:76.
13. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. Clinical Practice Guideline: The diagnosis and management of acute otitis media. The American Academy of Pediatrics. Pediatrics. 2013;131:e964-e999.
14. Ruohola A, Laine MK, Tähtinen PA. Effect of antimicrobial treatment on the resolution of middle-ear effusion after acute otitis media. JPIDS.2018:7:64-70.
15. Pirozzo S, Del Mar C. Chapter 27. Otitis media. In: Moyer VA, eds. Evidence based paediatrics and child health. London: BMJ Books;2000:238-47.
16. Teng CL. Antibiotic prescribing for upper respiratory tract infections in the Asia-Pacific region: A brief review. Malays Fam Physician. 2014;9(2):18–25.

APPENDICES

CHAPTER 1 ○ CHAPTER 3 ○ CHAPTER 4 ○ CHAPTER 5

APPENDICES – CHAPTER 1

Appendix 1.1. Alternative non-antibiotic treatment for acute otitis media

Appendix 1.2. Corticosteroids for acute respiratory and other infections

Appendix 1.1. Alternative non-antibiotic treatment for acute otitis media

Acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) [1].	A Cochrane review of very low to low quality evidence (3 trials; *n* = 327) assessing acetaminophen or NSAID, alone or in combination for AOM found that both paracetamol and ibuprofen as monotherapy were more effective than placebo in relieving pain at 48 hours: paracetamol versus placebo with the proportion of children with pain 10% versus 25% (1 trial; *n* = 148; relative risk (*RR*) 0.38, 95% confidence interval (CI) 0.17 to 0.85; *P* = 0.018; number needed to treat to benefit (NNTB) 7); ibuprofen versus placebo with proportion of children with pain 7% versus 25% (1 trial; n = 146; *RR* 0.28, 95% CI 0.11 to 0.70; *P* < 0.01; NNTB 6).
Decongestants and/or antihistamines [2].	A Cochrane review (15 trials; *n* = 2695) included RCTs of children with AOM who received either decongestant and/or antihistamine or control (no placebo in three trials) found: • A lower rate of persisting AOM only in the combined decongestant and antihistamine group in two weeks (5 trials; *n* = 482; *RR* 0.63; 95% CI 0.43 to 0.93; *P* = 0.019; I^2 = 0%; NNTB 10) • No significant benefit for early cure rates, resolution of the symptoms, or other complications • An increased risk of adverse effects in the intervention groups (five to eight times), particularly in the decongestant group.
Pneumococcal conjugate vaccine (PCV) [3].	A Cochrane review of moderate to high quality evidence from 11 RCTs (*n* = 60,733) of children aged up to 12 years found: • Most PCVs are effective in reducing the incidence of AOM if they are administered during early infancy (age < 1 year). • A 7-valent PCV with CRM197 as carrier protein (CRM197-PCV7) reduced the risk of all-cause AOM in low-risk infants (1 trial; *n* = 37,868 children; high quality evidence; relative risk reduction (*RRR*) 6%, 95% CI 4% to 9%).

	• Both CRM197-PCV7 and PCV7 with the outer membrane protein complex of Neisseria meningitidis serogroup B as carrier protein (OMPC-PCV7) reduced the risk of pneumococcal AOM (2 trials; *n* = 3328 children; high quality evidence; *RRR* 20% to 25%, 95% CI 7-11% to 31-37%). • A 11-valent PCV conjugated to protein D of *H. influenzae* (PHiD-CV11) reduced the risk of all-cause AOM (1 trial; *n* = 4968 children; high quality evidence; *RRR* 34%, 95% CI 21% to 44%). • Both PHiD-CV10 and PHiD-CV11 reduced the risk of pneumococcal AOM (2 trials; *n* = 12,327 children; high quality evidence; *RRR* 52% to 53%, 95% CI 16-37% to 63-74%). • Common adverse events found in the administration of PCV are mild local reactions (e.g., redness, swelling) and fever.
Probiotics [4].	A Cochrane review of RCTs of children aged up to 18 years found that probiotics (e.g., powder, drops, capsule, tablet, spray) containing Lactobacillus and Streptococcus reduced: • Incidence of AOM episode(s) during treatment (16 trials; *n* = 2961 children; moderate-quality evidence; *RR* 0.77, 95% CI 0.63 to 0.93; $P < 0.01$; $I^2 = 72\%$; NNTB 10). • Incidence of AOM among children who were not prone to AOM (11 trials; *n* = 2227 participants; moderate-quality evidence; *RR* 0.64, 95% CI 0.49 to 0.84; $P < 0.005$; $I^2 = 59\%$; NNTB 9) but not among children who were otitis prone • The risk of having other infection (11 trials; *n* = 3610 children; moderate-quality evidence; *RR* 0.75, 95% CI 0.65 to 0.87; $P < 0.001$; $I^2 = 64\%$; NNTB 12). There were no notable adverse events found in children received probiotics.
Ventilation tubes (grommets) [5].	A Cochrane review of very low to low quality RCTs of children with recurrent AOM (rAOM) showed that grommets either as a single

	therapy or as addition to adenoidectomy when compared to observation can reduce AOM recurrence at six months (1 trial; *n* = 95; *RR* 9.49, 95% CI 2.38 to 37.80; *P* < 0.005; NNTB 3) and 12 months (1 trial; *n* = 200; *RR* 1.41, 95% CI 1.00 to 1.99; *P* = 0.047; NNTB 7), as well as reduce the incidence rate of rAOM at six months (1 trial; *n* = 95; *MD* -1.50, 95% CI -1.99 to -1.01; *P* < 0.001) and 12 months (1 trial; *n* = 200; *MD* -0.55, 95% CI -0.17 to 0.93). Compared to placebo medication, grommets reduced the risk of having a new episode of rAOM (1 trial; *n* = 42; *RR* 3.64, 95% CI 1.20 to 11.04; *P* = 0.02; NNTB 3) and incidence rate of rAOM (1 trial; *n* = 42; *MD* -1.14, 95% CI -2.06 to -0.22; *P* = 0.016) at six months.
Topical analgesics [6,7].	A Cochrane review of RCTs and quasi-RCTs of children and adults (5 trials, *n* = 391) who came to primary care centre with intact eardrum AOM found that children who received an addition of topical analgesics to oral analgesics had a 50% pain reduction compared to placebo at 10 minutes (2 trials; *n* = 117; moderate-quality evidence; *RR* 2.13, 95% CI 1.19 to 3.80; *P* = 0.01; I^2 = 0%; NNTB 5) and 30 minutes (*RR* 1.43, 95% CI 1.12 to 1.81; *P* = 0.003; I^2 = 0%; NNTB 4) after the initial administration [6]. In a multicentre, randomised, parallel RCT (CEDAR trial) [91], children aged one to ten years with 24-hour preceding pain in a 1-week onset of AOM were randomised to receive either anaesthetic-analgesic ear drops (*n* = 38) or unblinded usual care (n = 36) in a two-arm trial (*n* = 74); or to receive anaesthetic-analgesic ear drops (*n* = 12) , placebo ear drops (*n* = 10) , or unblinded usual care (*n* = 10) in a three-arm trial (*n* = 32). In the two-arm trial, there were fewer children in the active ear drop group who received antibiotics by Day 8 (1/29 versus 9/30; *OR* 0.08, 95% CI 0.01 to 0.71, *P* = 0.023, NNTB 4. More children in the active ear drop group (*n* = 32) had a reduction of parent-report pain score (0-10 ear pain scale, higher scores represent more pain) compared to those in the usual care group (*n* = 30) at Day 2 (*MD* -1.62, 95% CI -2.86 to -0.39, *P* = 0.011), but not at

	Day 1. In the 3-arm trial, there was no difference in antibiotic consumption between children in the active ear drops and usual care groups (0/10 versus 2/8, *OR* 0.11, 95% CI 0.00 to 3.17, *P* = 0.201). There was no difference in pain score reduction between the active (*n* = 10) and placebo ear drop groups (*n* = 7) at Day 2 (*MD* 0.96, 95% CI -0.99 to 2.91, *P* = 0.312) nor in those in the active ear drop group compared to the usual care group (*n* = 9) (*MD* -1.90, 95% CI -3.85 to 0.05; *P* = 0.056). However, children who received placebo ear drops had a significant ear score reduction compared to those who received usual care (*n* = 9) (*MD* -2.86, 95% CI -4.46 to -1.25, *P* = 0.002). However, when 2-arm and 3-arm trials were combined, active ear drops were more likely to reduce antibiotic consumption compared to usual care (1/39 versus 11/38; OR 0.09, 95% CI 0.02 to 0.55, P = 0.009, NNTB 4). When two trials were combined, active ear drops (*n* = 42) reduced pain score compared to usual care (*n* = 39) at Day 2 (*MD* -1.70, 95% CI -2.74 to -0.66, *P* = 0.001). All results were consistent after adjusting for pain score at baseline. Although this study showed positive results for AOM, the sample size was small [7].
Influenza vaccines [8].	A Cochrane review of low to moderate quality RCTs found Influenza vaccines slightly reduced antibiotic use compared to placebo or no treatment (2 trials; *n* = 1223; *RR* 0.70, 95% CI 0.59 to 0.83; *P* < 0.001; I^2 = 0%; NNTB 9). However, the influenza vaccines increased the risk of fever (7 trials; *n* = 10,615; *RR* 1.15, 95% CI 1.06 to 1.24; *P* < 0.01; I^2 = 0%; NNTH 38) and rhinorrhoea (6 trials; *n* = 10,563; *RR* 1.17, 95% CI 1.07 to 1.29; *P* < 0.01; I^2 = 63%; NNTH 19). No serious adverse effects were found.
Xylitol [9].	A Cochrane review of moderate-quality RCTs and quasi-RCTs (5 trials; *n* = 3405) of children aged ≤ 12 years found that xylitol supplementation reduced the risk of AOM (3 trials; *n* = 1826; *RR* 0.75, 95% CI 0.65 to 0.88; *P* < 0.001; I^2 = 69%; NNTB 14) and

	reduced antibiotic initiation (1 trial; *n* = 306; *RR* 0.64, 95% CI 0.42 to 0.97; *P* = 0.03; NNTB 10) compared to control. This review also showed xylitol was not beneficial in reducing the incidence of AOM among healthy children during respiratory infections or among those who are prone to otitis. There was no significant difference in side effects (i.e., abdominal symptoms, rash) between the xylitol and placebo groups
Herbal medicines [10].	A systematic review of very low quality RCTs and quasi-RCTs (7 trials) of children and adults with AOM was conducted to assess the effectiveness of herbal medicine alone or combined with non-surgical treatment (e.g., antibiotics, decongestants and/or antihistamines) compared to other non-surgical treatment: • Two trials comparing a combination of herbal medicines of Longdan-xiegan (LDXG) decoction or pills or Shenlingbaizhu (SLBZ) powder and ampicillin with ampicillin alone showed that a combined herbal and antibiotics may improve AOM symptoms at Day 5 and Day 10. • One study comparing herbal medicine and conventional therapy with conventional therapy alone showed a symptom improvement at Day 14 (*n* = 119; *RR* 1.55, 95% CI 1.23 to 1.93; *P* = 0.0001). • A combination of LDXG pills and penicillin reduced symptom recovery time by two days compared to penicillin alone (1 trial; *n* = 137; *MD* -2.40, 95% *CI* -2.84 to -1.96; *p* < 0.0001). Symptom recovery time was also reduced by Eryanling decoction compared to cephalexin by eight days (1 trial; *n* = 102; *MD* −7.90, 95% CI -11.94 to -3.86; *P* = 0.0001). • One study comparing a combination of Sinupret and amoxicillin with amoxicillin alone showed there was significant improvement in fever at Day 7 (*RR* 1.23, 95% CI 1.03 to 1.46; *P* = 0.02), as well as nasal discharge at Day 3 (*RR* 2.89, 95% CI

	1.23 to 6.81; *P* = 0.02) and at Day 7 (*RR* 2.02, 95% CI 1.19 to 3.42; *P* = 0.009).
Nasal saline irrigations [11].	A pilot retrospective study using medical records of 173 children aged one to five years with history of rAOM comparing an intervention of supervised nasal saline irrigation (NSI) with non NSI showed that supervised NSI reduced the incidence of: • new episode of AOM (1.03 ± 0.14 versus 2.08 ± 0.16, *P* < 0.001). • spontaneous perforation of tympanic membrane (0.66 ± 0.11 versus 1.32 ± 0.16, *P* < 0.001). • the requirement for antibiotic treatment (1.48 ± 0.17 versus 2.59 ± 0.18, *P* < 0.001) during a 4-month follow-up visit.
Vitamin D supplementation [96-98]	Two case-control studies found that vitamin D (25(OH) vit D) deficiency was mostly found in children with recurrent AOM or otitis-prone children compared to healthy children, which indicates a low level of serum vitamin D is associated with the incidence and recurrence of AOM [12,13]. An RCT of children with a history of rAOM who received either vitamin D 1000 IU/day or placebo (58 versus 58, respectively) for four months showed fewer children in the Vit D group experienced at least one episode of AOM compared to the placebo group (26 versus 38; *RR* 0.68, 95% CI 0.49 to 0.96; *P* = 0.03; NNTB 5) in six months. This study concluded that vitamin D supplementation with a dose of 1000 IU/day was likely to improve vitamin D level to at least 30 ng/mL, which later would significantly reduce the incidence of AOM for children with vitamin D deficiency [14].

Appendix 1.2. Corticosteroids for acute respiratory and other infections.

Acute sinusitis [15].	A Cochrane review of low to moderate quality evidence from five RCTs of 1193 adults with acute sinusitis comparing oral corticosteroids with control (placebo or NSAIDs) showed short-term symptom resolution or improvement only in the oral corticosteroids as an addition to antibiotic group compared to the control group: at three to seven days (4 trials; *n* = 869; *RR* 1.40, 95% CI 1.08 to 1.81; *P* = 0.010; I^2 = 75%; NNTB 6) and at four to 14 days (4 trials; *n* = 945; *RR* 1.32, 95% CI 1.04 to 1.68; *P* = 0.022; I^2 = 84%; NNTB 7). There was no benefit in the use of corticosteroids as monotherapy.
Acute sore throat [16-18].	A Cochrane review of moderate to high quality evidence from eight RCTs of both children and adults (*n* = 743) with acute sore throat comparing oral corticosteroids as an addition to antibiotics with placebo showed those who received corticosteroids: (1) were more likely to have complete resolution of pain at 24 hours (4 trials; *n* = 286; *RR* 3.16; 95% CI 1.97 to 5.08; *P* < 0.001; I^2 = 44%; NNTB 4) and at 48 hours (3 trials; *n* = 209; *RR* 1.65; 95% CI 1.32 to 2.06; *P* < 0.001; I^2 = 0%; NNTB 3); (2) had a reduced mean time to onset of pain relief (6 trials; *n* = 609; mean difference (*MD*) -6.32 hours; 95% CI -9.29 to -3.35; *P* < 0.001; I^2 = 72%); and, (3) had a reduction in the mean time to complete resolution (5 trials; n = 500; *MD* -14.41 hours, 95% CI -24.99 to -3.84; *P* = 0.008; I^2 = 78%) [16]. A recent RCT of adults with acute sore throat without initial antibiotic treatment who received either single dose oral dexamethasone or placebo found that those who received corticosteroids: (1) were more likely to have complete symptom resolution at 48 hours (102/288 versus 75/277; *RR* 1.31, 95% CI 1.02 to 1.68; *P* = 0.030; NNTB 12), but not at 24 hours (65 versus 49; *RR* 1.28, 95% CI 0.92 to 1.78) and (2) were less likely to require antibiotic treatment (65/173 versus 46/169; *RR* 1.37, 95% CI 1.01 to 1.87; *P* = 0.046; NNTB 10) [17].

	A recent systematic review of moderate to high quality evidence from 10 RCTs of adults and children (*n* = 1426) with acute sore throat showed that there were more patients in the single low dose corticosteroid group who had complete resolution of pain at 24 hours (5 trials; *n* = 1049; *RR* 2.24; 95% CI 1.17 to 4.29; I^2 = 69%; NNTB 9) and 48 hours (4 trials; *n* = 1076; *RR* 1.48; 95% CI 1.26 to 1.75; I^2 = 3%; NNTB 8) [18].
Croup [19].	A Cochrane review of low to moderate quality evidence from RCTs (43 trials; *n* = 4565) of children aged up to 18 years with croup comparing any corticosteroids, as monotherapy or as an add-on, to placebo or other treatment found parenteral dexamethasone: • reduced croup symptoms at six hours (6 trials; *n* = 567; standardised mean difference (*SMD)* -0.62, 95% CI -1.17 to -0.08; *P* = 0.026; I^2 = 85%), 12 hours (5 trials; *n* = 323; *SMD* -0.85, 95% CI -1.55 to -0.15; *P* = 0.017; I^2 = 84%, and 24 hours (6 trials; *n* = 245; *SMD* -0.89, 95% CI -1.55 to -0.22, *P* = 0.009, I^2 = 81%). • reduced length of inpatient stay (6 trials; *n* = 328; *MD* -18.25, 95% CI -27.87 to -8.62; *P* < 0.001; I^2 = 41%) • improved croup at 12 hours (3 trials, *n* = 166; *RR* 1.52, 95% CI 1.06 to 2.18, *P* = 0.024; I^2 = 50%; NNTB 4) and at 24 hours (4 trials; *n* = 201; *RR* 1.39, 95% CI 1.05 to 1.84; *P* = 0.021; I^2 = 66%; NNTB 4).
Bronchiolitis [20].	An overview of four systematic review of 20 RCTs assessing the effects of any types of corticosteroids in children aged up to 24 months with bronchiolitis showed systemic corticosteroids only slightly reduced clinical scores using a respiratory distress assessment instrument compared to placebo or control (3 trials; *n* = 178; high-quality evidence; *SMD* -0.36, 95% CI -0.65 to -0.08) and did not reduce the length of stay for patients with/without mechanical ventilation, duration of mechanical ventilation, nor mortality based on low to moderate certainty evidence.

Community-acquired pneumonia [21,22].	In severe community-acquired pneumonia, a systematic review of nine RCTs showed that systemic corticosteroids reduced all-cause mortality compared to control (9 trials; *n* = 914; *OR* 0.63, 95% CI 0.42 to 0.95; *P* = 0.03; I^2 = 0%; NNTB 18) in adults, in which prednisolone or methylprednisolone significantly reduced total mortality compared to hydrocortisone (*OR* 0.37, 95% CI 0.19 to 0.72; *P* = 0.04). In addition, systemic corticosteroids reduced the duration of ICU stay (6 trials; *n* = 287; *MD* -2.52 days, 95% CI -4.88 to -0.15; *P* = 0.04; I^2 = 59%). There were no differences on adverse events (i.e., hyperglycaemia, gastrointestinal haemorrhage, cardiac events) between the corticosteroids and control groups [21]. One Cochrane review of moderate to high-quality evidence from 17 RCTs showed children (four RCTs; *n* = 301) with bacterial community-acquired pneumonia who received systemic corticosteroids compared to those received placebo or no treatment, had reduction of early clinical failure rates (2 trials; *n* = 88; high-quality evidence; *RR* 0.41, 95% CI 0.24 to 0.70; *P* < 0.01; I^2 = 25%; NNTB 3), as well as reduction of time to clinical cure (3 trials; *n* = 225; *MD* -1.57 days, 95% CI -2.55 to -0.60; *P* < 0.01; I^2 = 80%) [22]. One common adverse event found in adults was hyperglycaemia (7 trials; *n* = 1578; *RR* 1.72, 95% CI 1.38 to 2.14; I^2 = 21%; NNTH 10), but no other adverse events were found.
Wheezing [23,24].	An RCT of 74 children aged three to 23 months with the first acute rhinovirus-induced wheezing (moderate to severe) comparing oral prednisolone at dose of 2 mg/kg/day and placebo for three days showed prednisolone reduced the duration of cough (6.2 ± 3.6 versus 8.9 ± 3.7 days; *MD* -2.8 days, 95% CI -4.5 to -1.0, *P* = 0.002), noisy breathing (5.3 ± 3.3 versus 7.3 ± 3.9 days; *MD* -2.0, 95% CI -3.6 to -0.29; *P* = 0.02), and rhinitis (5.5 (2-9) versus 8.5 (6-11.5) days; *MD* -3, 95% CI -5 to -1; *P* = 0.008) at two weeks after discharge [23]. An recent RCT assessing oral prednisolone (1 mg/kg/day) versus placebo for three days in 605 children aged 24 to 72 months with

	virus-induced wheezing showed prednisolone reduced the length of stay at the emergency department (ED) compared to control (370 (121-709) versus 540 (124-971) minutes; unadjusted ratio of geometric mean 0.79, 95% CI 0.64 to 0.97, P = 0.023) [24]. There were no significant differences in adverse events between the two groups in these two studies [23,24].
Influenzae [25].	A Cochrane review of very low-quality evidence from 19 observational studies (n = 3459) assessing effects of corticosteroids as an additional therapy for patients with influenzae or influenzae-like illness showed corticosteroids may increase mortality (13 studies, n = 1917; *OR* 3.06, 95% CI 1.58 to 5.92, P < 0.001; I^2 = 80%).
Acute bacterial meningitis [26].	In acute bacterial meningitis, a Cochrane review of moderate to high quality evidence from 25 RCTs (n = 4121 children and adults) testing any types of corticosteroids as an addition to antibiotic treatment showed those who received corticosteroids were less likely to have severe hearing loss (17 trials; n = 2437; *RR* 0.67; 95% CI 0.51 to 0.88; P = 0.004; I^2 = 0%; NNTB 31) and any hearing loss (20 trials; n = 2785; *RR* 0.74; 95% CI 0.63 to 0.87; P < 0.001; I^2 = 24%; NNTB 19), as well as neurological sequelae (13 trials; n = 1756; *RR* 0.83, 95% CI 0.69 to 1.00; P = 0.046; I^2 = 0%; NNTB 27) compared with those without. However, corticosteroids did not significantly reduced mortality rates.
Sepsis [27].	A Cochrane review of low quality evidence from 33 RCTs (n = 4268) that included some children but mostly adults with sepsis showed long-course of low dose corticosteroids reduced all-cause mortality rates at 28 days (22 trials; n = 2266; *RR* 0.87, 95% CI 0.78 to 0.97; P = 0.013; I^2 = 16%; NNTB 25). Corticosteroids also ICU stay duration (12 trials; n = 1384; *MD* -1.68 days, 95% CI -3.27 to -0.09; P = 0.038; I^2 = 31%). Patient who received corticosteroids had significantly more adverse events of hyperglycaemia (13 trials; n = 2081; *RR* 1.26,

	95% CI 1.16 to 1.37; $P < 0.0001$; $I^2 = 26\%$; NNTH 12) and hypernatremia (3 trials; $n = 805$; *RR* 1.64, 95% CI 1.28 to 2.09; $P < 0.0001$; $I^2 = 0\%$; NNTH 9).

REFERENCES

1. Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AGM, Damoiseaux RAMJ. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD011534. DOI: 10.1002/14651858.CD011534.pub2.
2. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD001727. DOI: 10.1002/14651858.CD001727.pub4.
3. Fortanier AC, Venekamp RP, Boonacker CWB, Hak E, Schilder AGM, Sanders EAM, et al. Pneumococcal conjugate vaccines for preventing acute otitis media in children. Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD001480. DOI: 10.1002/14651858.CD001480.pub5.
4. Scott AM, Clark J, Julien B, Islam F, Roos K, Grimwood K, et al. Probiotics for preventing acute otitis media in children. Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD012941. DOI: 10.1002/14651858.CD012941.pub2.
5. Venekamp RP, Mick P, Schilder AGM, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD012017. DOI: 10.1002/14651858.CD012017.pub2.
6. Foxlee R, Johansson AC, Wejfalk J, Dooley L, Del Mar CB. Topical analgesia for acute otitis media. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005657. DOI: 10.1002/14651858.CD005657.pub2.
7. Hay AD, Downing H, Francis NA, Young GJ, Clement C, Harris SD, et al. Anaesthetic-analgesic ear drops to reduce antibiotic consumption in children with acute otitis media: the CEDAR RCT. Health Technol Assess. 2019 Jul;23(34):1-48. doi: 10.3310/hta23340.
8. Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD010089. DOI: 10.1002/14651858.CD010089.pub3.
9. Azarpazhooh A, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD007095. DOI: 10.1002/14651858.CD007095.pub3.
10. Son MJ, Kim YE, Song YI, Kim YH. Herbal medicines for treating acute otitis media: A systematic review of randomised controlled trials. Complement Ther Med. 2017 Dec;35:133-139. doi: 10.1016/j.ctim.2017.11.001. Epub 2017 Nov 9.

11. Torretta S, Pignataro L, Ibba T, Folino F, Fattizzo M, Marchisio P. Supervised nasal saline irrigations in otitis-prone children. Front. Pediatr. 2019;7:218. doi: 10.3389/fped.2019.00218.
12. Cayir A, Turan MI, Ozkan O, Cayir Y, Kaya A, Davutoglu S, et al. Serum vitamin D levels in children with recurrent otitis media. Eur Arch Otorhinolaryngol. 2014 Apr;271(4):689-93. doi: 10.1007/s00405-013-2455-7. Epub 2013 Mar 30.
13. Cayir A, Turan MI, Ozkan O, Cayir Y. Vitamin D levels in children diagnosed with acute otitis media. J Pak Med Assoc. 2014 Nov;64(11):1274-7.
14. Marom T, Marchisio P, Tamir SA, Torretta S, Gavriel H, Esposito S. Complementary and Alternative Medicine Treatment Options for Otitis Media A Systematic Review. Medicine. 2016;95(6):e2695. DOI: 10.1097/MD.0000000000002695.
15. Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar CB, Perera R, et al. Systemic corticosteroids for acute sinusitis. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD008115. DOI: 10.1002/14651858.CD008115.pub3.
16. Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ. Corticosteroids as standalone or add-on treatment for sore throat. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD008268. DOI: 10.1002/14651858.CD008268.pub2.
17. Hayward GN, Hay AD, Moore MV, Jawad S. Williams N. Effect of oral dexamethasone without immediate antibiotics vs placebo on acute sore throat in adults a randomized clinical trial. JAMA. 2017;317(15):1535-1543.
18. Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, Papola D, Lytvyn L, Vandvik PO, et al. Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. BMJ. 2017;358:j3887.
19. Gates A, Gates M, Vandermeer B, Johnson C, Hartling L, Johnson DW, et al. Glucocorticoids for croup in children. Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD001955. DOI: 10.1002/14651858.CD001955.pub4.
20. Alarcón-Andrade G, Cifuentes L. Should systemic corticosteroids be used for bronchiolitis? Medwave 2018 May-Jun;18(3):e7206 doi: 10.5867/medwave.2018.03.7206.
21. Huang J, Guo J, Li H, Huang W, Zhang T. Efficacy and safety of adjunctive corticosteroids therapy for patients with severe community-acquired pneumonia: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(13):e14636. doi: 10.1097/MD.0000000000014636.

22. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD007720. DOI: 10.1002/14651858.CD007720.pub3.
23. Jartti T, Nieminen R, Vuorinen T, Lehtinen P, Vahlberg T, Gern J, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. J Allergy Clin Immunol. 2015;135:691-8.
24. Foster SJ, Cooper MN, Oosterhof S, Borland ML. Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomised, double-blind, placebo-controlled trial. Lancet. 2018;6:97-106.
25. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD010406. doi: 10.1002/14651858.CD010406.pub2.
26. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015;9:CD004405. doi: 10.1002/14651858.CD004405.pub5.
27. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD002243. DOI: 10.1002/14651858.CD002243.pub3.

APPENDICES – CHAPTER 3

Appendix 3.1. Information and consent form

Appendix 3.1. Information and consent form

INFORMATION FORM FOR POTENTIAL PARTICIPANT

Research title : The management of acute otitis media in children in DKI Jakarta, Depok, and Bekasi
Researcher : Prof. Dr. dr. XX

Dear Mr/Mrs/Ms/Miss,

We, researchers from [ ] and [ ], is currently conducting survey study on the management of acute otitis media (AOM) in children in Jakarta, Depok, and Bekasi.

This study aims to determine and identify current clinical practices, attitudes and behaviors of physicians (GPs, ENT specialist, and pediatricians) in the management of acute otitis media in children, and to identify the incidence of acute otitis media in children at various health care facilities in DKI Jakarta, Depok, and Bekasi. In addition, we also want to identify potential interests of the above practitioners to participate in further clinical trial regarding the use of corticosteroids as an alternative intervention in the treatment of acute otitis media in children.

The data obtained from this study will be useful to achieve an overview of current clinical practices, attitudes, and behaviors of the physicians in the management of acute otitis media in children, particularly regarding to the use of antibiotics, as well as the incidence of acute otitis media in children in DKI Jakarta, Depok, and Bekasi. It also will be used as a baseline data for the future clinical research on the role of corticosteroids in the management of acute otitis media in children, as it can be used as an alternative therapy to antibiotics in certain groups of children with acute otitis media, in order to reduce antibiotic resistance rates.

In this study we will distribute questionnaires consist of the initial data (anonymous), current clinical practice, attitudes and behaviour, the case scenarios, as well as your potential interest to participate in clinical research on the role of corticosteroids in the treatment of acute otitis media in children that will be held on February 2017 to February 2018. If you are interested to participate, we also will obtain some additional information of biographical data, employment, and education columns.

This study is voluntary. You are free to decide whether are willing to participate in this study or not, without any further affect.

All data in this study will be kept confidential so it is not possible for others to connect it with you. All provided information will only be used for research purposes. It will not affect the assessment of your director and other relevant (authorized) committee in your institution. The result of such information will be presented in the form of aggregate data covering all participants, instead of personal data of each participant. You are free to decide whether you are willing to participate in this study or not. You have the opportunity to ask all unclear information related to this study.

If you require further information regarding this survey study, please do not hesitate to contact Prof. Dr. dr. SS at [ ] [ ] Phone number [ ], or email: [ ].

Thank you for your kind attention and contribution.

Researcher,

Prof. Dr. dr. SS

dr. RR

THE CONSENT FORM

I, hereby undersigned:

Name :……..

Age : …… years old.

Address: ……..

……..

After receiving information regarding this study from the researcher, herewith I declare the agreement / disagreement *) to participate as a respondent in this study entitled: **" The management of acute otitis media in children in DKI Jakarta, Depok, and Bekas**i **"**

This statement was made without coercion from any party.

Who provided statement above,	Researcher,
Name: ……	Name: ……
Date: ……..	Date: ……..

**Please strikethough your incorrect option*

APPENDICES – CHAPTER 4

Appendix 4.1. Study protocol

Appendix 4.2.Case report forms

Appendix 4.3. Manual of operations

Appendix 4.4. Training slides

Appendix 4.1. Study protocol

Oral Prednisolone for Acute otitis media in chiLdren:

A pilot pragmatic, randomised, open-label, single-blind, controlled study (OPAL Study)

Centre for Research in Evidence-Based Practice
Faculty of Health Sciences and Medicine Bond University
Queensland, Australia

Clinical Epidemiology and Evidence-Based Medicine
Dr Cipto Mangunkusumo Hospital
Faculty of Medicine Universitas Indonesia
Jakarta, Indonesia

Administrative information

Protocol title

Oral **P**rednisolone for **A**cute otitis media in chi**L**dren: a pilot pragmatic randomised open-label single-blind study (**OPAL study**)

Authors

Respati W. Ranakusuma, MD, ORL

Dr. Amanda McCullough, PhD, PGCHET, BSc (Hons)

Associate Professor Elaine Beller, BSc, MAppStat

Professor Christopher Del Mar, FAFPHM, MA, MD, FRACGP, BSc

Professor Dr. Sudigdo Sastroasmoro, MD, PhD, Paed.

Eka Dian Safitri, MD, ORL

Yupitri Pitoyo, MD, ORL

Widyaningsih, MPH

Arie Sulistyowati, MD, MSc, Paed.

Table of Contents

Trial registration

Registry name: http://www.ANZCTR.org.au/ACTRN12618000049279.aspx

The World Health Organisation Trial Registration Data set

Primary Registry and Trial Identifying Number	ACTRN12618000049279
Date of Registration in Primary Registry	16 January 2018
Secondary Identifying Numbers	-
Source(s) of Monetary or Material Support	Self-funded research
Primary Sponsor	Respati W. Ranakusuma, MD, ORL Centre for Research in Evidence-Based Practice Faculty of Health Sciences and Medicine Bond University, QLD, Australia 14 University Drive, Robina 4226, Queensland Phone number: +61424957129 (Australia) / +6228111012185 (Indonesia) Email: rranakus@bond.edu.au
Secondary Sponsor(s)	None
Contact for Public Queries	Respati W. Ranakusuma, MD, ORL Centre for Research in Evidence-Based Practice Faculty of Health Sciences and Medicine Bond University, QLD, Australia 14 University Drive, Robina 4226, Queensland Phone number: +61424957129 (Australia) / +6228111012185 (Indonesia) Email: rranakus@bond.edu.au
Contact for Scientific Queries	Respati W. Ranakusuma, MD, ORL Email: rranakus@bond.edu.au Phone number: +61424957129 (Australia) / +6228111012185 (Indonesia) Centre for Research in Evidence-Based Practice Faculty of Health Sciences and Medicine Bond University, QLD, Australia 14 University Drive, Robina 4226, Queensland Email: OPAL.study@bond.edu.au Phone number: (+61) 7 559 51588
Public Title	Oral prednisolone for acute middle ear infection in children
Scientific Title	Oral prednisolone for acute otitis media in children: a pilot pragmatic randomised open-label single-blind study (OPAL study)
Countries of recruitment	Indonesia
Health Condition(s) or Problem(s) Studied	Acute otitis media in children
Intervention(s)	Intervention Name: • Active intervention: Prednisolone tablet • Active comparator: None Intervention Description: • Prednisolone tablet with doses based on range of age for five days: ○ 6 months – <2 years: 10 mg/day ○ 2 – <6 years: 20 mg/day ○ 6 – 12 years: 30 mg/day • None
Key Inclusion and Exclusion Criteria	Ages eligible for study: 6 months to 12 years Sexes eligible for study: both males and females Accepts healthy volunteers: no Inclusion criteria: • children (6 months – 12 years) with acute otitis media, defined as a current onset within 48 hours of ear-related symptoms (e.g. ear pain, ear tugging/rubbing or irritability) and if possible to assess, otoscopic findings of acute inflammation (e.g. erythema) and middle ear effusion (e.g. bulging, air-fluid level) Exclusion criteria: • children with major and severe medical conditions (e.g. heart failure, kidney failure) • immunocompromised children (e.g. HIV, children receiving cancer treatment)

	• children with congenital malformations and/or syndromes (e.g. cleft palate, Down's syndrome) • children with high risk of risk of strongyloidiasis infection • children with ear ventilation tube(s) • children who had exposed to persons with varicella (chicken pox) or active Zoster infection in the past 3 weeks without any prior varicella immunisation or infection • children who have taken systemic (i.e. oral, injection) or topical steroids in the preceding four weeks • children who have taken antibiotics in the preceding two weeks; a • children who are hypersensitive to prednisolone or prednisone, or other corticosteroids.
Study Type	Type of study: interventional Method of allocation: stratified, randomised Masking: open-label, single-blind (outcome assessor) Assignment: parallel Purpose: Efficacy Phase III
Date of first enrolment	01 January 2018
Target sample size	60 children
Recruitment status	Pending (not started): participants are not yet being recruited or enrolled at any site
Outcome(s)	(1) Outcome Name: Recruitment rates Metric/method of measurement: Informed consent form and case report forms (CRFs) The timepoint(s) of interest: Baseline visit (visit-0) (2) Outcome Name: The success of the study procedures Metric/method of measurement: CRFs (i.e. eligibility and randomisation form, outcomes form) The timepoint(s) of interest: Baseline visit (visit-0) (3) Outcome Name: Ability to measure planned outcomes in main study Metric/method of measurement: CRFs (i.e. eligibility and randomisation form, outcomes form) and symptom diary (e.g. Visual Analogue Scale/VAS and Acute Otitis Media – Severity of Symptoms Scale/AOM-SOS), and feedback form The timepoint(s) of interest: Baseline visit, visit-1 (day-3 to-5), visit-2 (day-7 to -9), day3, visit-3 (day-3 to -40), and visit-4 (day-90 to -100) (4) Outcome Name: Compliance to study and study drug Metric/method of measurement: CRF (i.e. outcomes form), the symptom diary, and number of left-over drug The timepoint(s) of interest: Visit-1 (day-3 to-5), visit-2 (day-7 to -9), day3, visit-3 (day-3 to -40), and visit-4 (day-90 to -100) (5) Outcome Name: The verification of sample size calculation for main study Metric/method of measurement: CRFs (i.e. eligibility and randomisation form) The timepoint(s) of interest: Baseline visit (visit-0)

Protocol version

Protocol version No.	Date issued
Protocol OPAL Study Version 1.0.0 (V1.0.0)	27 July 2017
Protocol OPAL Study Version 1.1.0 (V1.1.0)	17 October 2017

Protocol Amendment Number: AM1.0

Amendment history:

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Detail of changes made
Amendment No. 1.0	Protocol V1.1.0	17 October 2017	Respati W Ranakusuma	1. <u>The modification of the form of trial drug</u> We planned to use prednisolone liquid. Due to administrative issues where the proposed pharmaceutical manufacturer was unable to share confidential documents that were required for importing the trial drug to Indonesia, we therefore will use prednisolone tablet for this trial. The pharmacist will crush the prednisolone tablets and mix it with sweetener. The crushed tablet will be packed in daily paper-package. The parents will mix the crushed tablet with juice or honey. This method is commonly practiced in Indonesia, particularly for paediatric patients. 2. <u>The duration of the trial drug use</u> We planned to give prednisolone for seven days. Although 7-day duration of corticosteroid use is considered as a short-term use, we will reduce its duration to five days to minimise the potential harms caused by corticosteroids.

Funding

This research is supported by self-funding of the principal investigator (Dr. Respati W. Ranakusuma, ORL).

We will purchase the trial drug, prednisolone tablets, from PT Pratapa Nirmala, Tangerang, Indonesia. This pharmaceutical manufacturer is not linked to this study and does not have authority over any procedural implementation, scientific process, or decision in the study.

Roles and responsibilities

Protocol contributions

Name	Affiliation	Role of protocol contributors
Dr. Respati W. Ranakusuma, ORL ENT surgeon, PhD candidate Telp: +61 424 957 129 / +62 8111 012 185 Fax: N/A Email: rranakus@bond.edu.au / respati.ranakusuma@ceebm.org	• Centre for Research in Evidence-Based Practice (CREBP) Faculty of Health Sciences and Medicine, Bond University 14 University Drive, Robina QLD 4226 Australia • Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 Indonesia	Initiated the study design and methodology; developed the protocol including case report forms (CRFs), informed consent, and symptom diary
Dr. Amanda McCullough, PhD, PGCHET, BSc (Hons) Epidemiologist, expert in acute respiratory infections and antibiotic resistance Telp: +61 7 559 55204 Fax: N/A Email: amccullo@bond.edu.au	Centre for Research in Evidence-Based Practice (CREBP) Faculty of Health Sciences and Medicine, Bond University, 14 University Drive, Robina QLD 4226 Australia	Initiated the study design from the clinical epidemiologic perspective; refined the protocol including case report forms (CRFs), informed consents, and symptom diary
Associate Professor Elaine Beller, BSc, MAppStat Clinical trialist, biostatistician Telp: +61 7 559 55523 Fax: N/A Email: ebeller@bond.edu.au	Centre for Research in Evidence-Based Practice (CREBP) Faculty of Health Sciences and Medicine, Bond University, 14 University Drive, Robina QLD 4226 Australia	Initiated the study design and methodology from the clinical trialist and biostatistician perspectives; refined the protocol including case report forms (CRFs), informed consents, and symptom diary
Professor Christopher Del Mar, FAFPHM, MBBChir, MA, MD, FRACGP, BSc Epidemiologist, evidence-based practitioner, expert in acute respiratory infection and antibiotic resistance Telp: +61 7 559 52504 Fax: N/A Email: cdelmar@bond.edu.au	Centre for Research in Evidence-Based Practice (CREBP) Faculty of Health Sciences and Medicine, Bond University, 14 University Drive, Robina QLD 4226 Australia	Initiated the study design from the clinical perspective; refined the protocol including case report forms (CRFs), informed consents, and symptom diary
Professor Dr. Sudigdo Sastroasmoro, PhD, Paed Paediatrician, epidemiologist, evidence-based practitioner Telp: +62 21 316 1760 Fax: N/A Email: sudigdo1947@gmail.com	• Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 Indonesia • Department of Child Health Faculty of Medicine Unit, Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital DIponegoro 71 Jakarta 10430 Indonesia	Provided advice in paediatric perspectives, supervising the trial in Jakarta

Contact information of trial sponsor or funder(s)

Name	Contact information	Role of study sponsor and funders
Dr. Respati W. Ranakusuma, ORL	• Centre for Research in Evidence-Based Practice (CREBP) Faculty of Health Sciences and Medicine, Bond University 14 University Drive, Robina QLD 4226 Australia • Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430, Indonesia	She is the principal investigator

Contact information of research team and others overseeing the trial

Name	Affiliation	Roles and responsibilities
Associate Investigators		
Dr. Eka Dian Safitri, ORL ENT surgeon Telp: +62 21 316 1760 Fax: N/A Email: ekadian.safitri@ceebm.org	Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 – Indonesia	(1) involved in the development of tympanometry study; (2) providing training related to using and interpreting tympanometry to physicians, nurses, and tympanometry technicians
Dr. Yupitri Pitoyo, ORL ENT surgeon Telp: +62 21 316 1760 Fax: N/A Email: yupitri.pitoyo@ceebm.org	Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 – Indonesia	Recruiting secondary and tertiary healthcare centres including the physicians and nurses
Dr. Arie Sulistyowati, MSc, Paed. Paediatrician, epidemiologist Telp: +62 21 316 1760 Fax: N/A Email: arie.sulistyowati@ceebm.org	Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 – Indonesia	Providing advice and expertise in terms of paediatric patients
Widyaningsih, MPH Public Health, qualitative study expert Telp: +62 21 316 1760 Fax: N/A Email: widyaningsih.ade@ceebm.org	Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 – Indonesia	(1) submitting a research ethics application to the Indonesian Medical Research Ethics Committee; (2) recruiting primary healthcare centres including the physicians and nurses
Research Coordinator		
Dr. Respati W. Ranakusuma, ORL ENT surgeon, PhD candidate Telp: +62 8111 012 185 Fax: N/A Email: rranakus@bond.edu.au / respati.ranakusuma@ceebm.org	Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 – Indonesia	
Co-investigators		
Dr. Tri Juda Airlangga H, ORL ENT surgeon Telp: +6221 1500 135 Fax: N/A Email: airlanggamd@gmail.com	Department of Ear, Nose, and Throat Head and Neck Surgery Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Central Jakarta 10430 – Indonesia	(1) Recruiting patients (2) Coordinating patient recruitment among other clinicians in the hospital
Dr. Yulvina, ORL ENT surgeon Telp: +6221 470 1133 Fax: N/A Email: yulie_dj@yahoo.com	Department of Ear, Nose, and Throat Head and Neck Surgery Persahabatan General Hospital Jl. Persahabatan Raya 1 East Jakarta 13230 – Indonesia	(1) Recruiting patients (2) Coordinating patient recruitment among other clinicians in the hospital

Dr. Evita Fitria Edyani, ORL ENT surgeon Telp: +6221 344 1008 Fax: N/A Email: evitafitria@yahoo.com	Department of Ear, Nose, and Throat Head and Neck Surgery Gatot Subroto Army Hospital Jl. Dr Abdul Rahman Saleh 24 Central Jakarta 10410 – Indonesia	(1) Recruiting patients (2) Coordinating patient recruitment among other clinicians in the hospital
Dr. Yupitri Pitoyo, ORL ENT surgeon Telp: +6221 884 2121 Fax: N/A Email: yupitri.pitoyo@ceebm.org	Department of Ear, Nose, and Throat Head and Neck Surgery Hermina Bekasi Hospital Jl. Kemakmuran 39, South Bekasi West Java 17141 – Indonesia	(1) Recruiting patients (2) Coordinating patient recruitment among other clinicians in the hospital
Dr. Respati W. Ranakusuma, ORL ENT surgeon Telp: +6221 2937 8939 Fax: N/A Email: rranakus@bond.edu.au	Department of Ear, Nose, and Throat Head and Neck Surgery Antam Medika Hospital Jl. Pemuda 1A East Jakarta 13210 – Indonesia	(1) Recruiting patients (2) Coordinating patient recruitment among other clinicians in the hospital
Dr. Eka Dian Safitri, ORL ENT surgeon Telp: +6221 425 0451 Fax: N/A Email: ekadian.safitri@ceebm.org	Department of Ear, Nose, and Throat Head and Neck Surgery Jl. Cempaka Putih Tengah I/1 Central Jakarta 10510 – Indonesia	(1) Recruiting patients (2) Coordinating patient recruitment among other clinicians in the hospital
Dr. Hably Warganegara, ORL ENT surgeon Telp: +6221 390 0002 Fax: N/A Email: hablywarganegara@gmail.com	Proklamasi Ear, Nose, Throat (ENT) Centre Jl. Proklamasi 43 Central Jakarta 10230 – Indonesia	(1) Recruiting patients (2) Coordinating patient recruitment among other clinicians in the hospital
Data Manager		
Respati W. Ranakusuma, MD, ORL ENT surgeon, PhD candidate Telp: +61 424 957 129 / +62 8111 012 185 Fax: N/A Email: rranakus@bond.edu.au / respati.ranakusuma@ceebm.org	Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia Jl. Diponegoro 71 Jakarta 10430 Indonesia	

CHAPTER 1 – INTRODUCTION

1.1 Background and rationale

1.1.1 Background

Antibiotic resistance, a major global threat, impacts more than two million people with illness and accounts for 23 thousand deaths annually in the United States [1]. One of the key drivers of the development of antibiotic resistance is antibiotic prescribing [2]. Antibiotics are mostly prescribed for common diseases, such as acute respiratory infections (ARIs) [3]. One of the ARIs commonly found in paediatric population with high antibiotic prescribing is acute otitis media [4,5]. In East Jakarta, Indonesia, the prevalence of AOM in children (< 18 years) was 5.4% [6]. In contrast, in Australia, there were an average of 35 new AOM cases reported by general practitioners per year (April 2010 – March 2015) [7].

Acute otitis media (AOM) is characterised by rapid onset of symptoms (e.g. earache, ear tugging/rubbing, irritability), middle ear effusion (e.g. bulging, immobile tympanic membrane, air fluid level), and acute inflammation (e.g. erythema) [8]. Almost three quarters of children have an episode of AOM in their first five years of life, with the peak incidence at the age of six to 12 months [9,10]. Guidelines recommend close monitoring for 48 hours (expectant observation) along with adequate pain management for mild AOM (e.g. mild symptoms, fever < 39°C) [8]. Children with severe symptoms, young age (< 2 years) with bilateral AOM, and AOM with tympanic membrane perforation are more likely to benefit from antibiotic treatment [11]. A high rate of antibiotic prescription for AOM is evident. Eighty-nine per cent new AOM cases were managed by antibiotics in Australia during 2010 to 2015 [7]. In Indonesia, a survey study using clinical scenarios, demonstrated that up to 88% of physicians would prescribe antibiotics for mild case of AOM. Unclear clarification of antibiotic use in the Indonesian practice guideline for AOM in the primary care may contribute to this [12]. The option of using antibiotics also must be balanced against the risks, such as adverse effects (e.g. vomiting, diarrhoea, rash) and antibiotic resistance [13,14].

1.1.2 Rationale for the proposed study

Prednisolone

Reducing antibiotic use is crucial to lowering the risk of antibiotic resistance. One of the methods is to use an alternative treatment that does not involve antibiotics. The current alternative treatments (i.e. ear drops, herbal products, probiotics, zinc, decongestants) demonstrate insufficient evidence on their benefits for AOM [15,16]. It is important to understand the pathophysiology of AOM, which is an inflammatory process involving both cellular and chemical inflammatory mediators (i.e. cytokines, chemokines, mast cells, prostaglandins, leukotrienes) in the middle ear. These inflammatory mediators contribute in altering the vascular permeability, increasing mucous glycoprotein secretion, as well as stimulating the chemotaxis process, the activity of epithelial secretion and other mediators [17]. An intervention suppressing this inflammatory process, could have an important role in the resolution of AOM. Corticosteroids suppress the inflammation process by inhibiting the mediators and cytokines characteristic of AOM, the recruitment of leukocytes and monocyte-macrophages into affected areas, and the synthesis and/or release of numerous inflammatory mediators and cytokine, and also reducing vascular permeability [18].

Corticosteroids are produced in the adrenal cortex. Cortisol (glucocorticoids), one of the most common corticosteroids, is responsible for anti-inflammatory effects. The production of glucocorticoids is controlled by hypothalamus, pituitary, and adrenal (HPA) axis. Corticosteroid treatment may affect the production of natural corticosteroid by suppressing the HPA axis [19,20]. We have identified prednisolone is commonly used and safe in the treatment of inflammatory and autoimmune diseases in children. Prednisolone, a synthetic intermediate-acting glucocorticoid with a biological half-life of 12 to 36 hours, is commonly used in the treatment of inflammatory and autoimmune diseases in children. Although prednisolone has a lesser anti-inflammatory potency compared to other common corticosteroids (i.e. methylprednisolone, dexamethasone), but it has lesser growth effect which is one of the concerning issues in the disease management in paediatric population [19].

We will give prednisolone at a dose of 1 mg/kg to 2 mg/kg body weight based on age category, once daily for five days. As there is a wide therapeutic dose window for prednisolone, this will enable us to operationalise the dose as 10 mg/day for children aged six months less than two years; 20 mg/day for children aged two to five years; and 30 mg/day for children aged six to 12 years, simplifying both randomisation and dosage instructions. The current treatment for AOM does not include corticosteroids in the guidelines. Therefore, we determined the dose and duration of prednisolone based on the doses regularly used in the paediatric otitis media trials and regular dose for other inflammatory and infection diseases in children based on the international and national practice guidelines, such as bronchial asthma, juvenile rheumatoid arthritis, and acute bacterial meningitis [21-25]. The duration of corticosteroid use in otitis media trials varies between three to seven days [18, 26-28]. An animal study [29] using mice infected with Streptococcus pneumoniae and non-typeable H. influenzae (NTHi) bacteria demonstrated that most of AOM-related cytokines peaks at three to six hours after the infections (interleukin-6/IL-6, interleukin-1 alpha/IL-1α, tumor necrosis factor alpha/TNF-α) an at six hours to three days (interleukin-10/IL-10). In general, these cytokines will be progressively reduced between the fourth to sixth day of infection and the acute otitis media will be resolved after the sixth day [29]. Therefore, we will give the prednisolone for five days in order to boost the natural resolution mechanism in AOM cases and to minimize the potential harms of corticosteroid use even though 7-day duration is still regarded as short-term use.

A single daily dose is preferable over divided doses to prevent the hypothalamic-pituitary-adrenal (HPA) axis suppression. Prednisolone should be given in a single dose at 6 to 8 am in the morning to mimic the normal diurnal rhythm of cortisol production [19,20] and because it is also more convenient for children and parents in the study to just take a trial drug once a day.

Potential harms

Despite the favourable effect of corticosteroids for inflammation, there are still several potential adverse effects related to its short-term use. A systematic review identified side effects of short-course of corticosteroids (less than two weeks) in children, such as gastrointestinal disturbances (i.e. vomiting, gastritis, nausea), behavioural changes (i.e. mood swings, nervousness), HPA axis suppression, increased blood pressure, hyperglycaemia, weight gain, and decreased bone mineralisation [30]. Even though there were more children experiencing these side effects compared to placebo, the included studies used a diverse of corticosteroids' types and duration, as well as the results were uncertain and include both important beneficial and harmful effects of

corticosteroid. Vomiting and behavioural disturbances (i.e. anxiety, aggressive behaviour) are the common side effects [30].

Regarding vomiting, there were three studies comparing prednisolone to placebo or control (other type of corticosteroids). A good quality RCT [31] included children aged 10 to 60 months with virus-induced wheezing who received a single dose of inhaled albuterol. These children then were randomly allocated to either prednisolone (10 mg oral prednisolone for children aged 2 years and younger; 20 mg for aged >2 years) group (n=343) or placebo (n=344). No significant differences on clinical outcomes (e.g. time to hospital discharge) or adverse effects between two groups were detected. There was one child from prednisolone group who vomited that required the discontinuation of the prednisolone [odds ratio (OR) 3.02 (95% confidence interval (CI) 0.12 to 74.33; p-value=0.50; number needed to harm (NNTH; number of children who are treated with prednisolone that will result in one additional event of side effects) = 34 children)] [31]. One study [32] on children aged one to 17 years with acute asthma presenting to the emergency department (ED). The children received a dose of inhaled albuterol and either a single dose of oral prednisone 2 mg/kg (n=41) or placebo (n=40). There was no a significant difference in the incidence of vomiting after taking the prednisone between the prednisone group (n=3; 7.3%) and the placebo group (n=1; 2.5%) [OR 3.08 (95% CI 0.31 to 30.92; p-value=0.34; NNH=21)] [32]. The same author with similar inclusion criteria [33] demonstrated a significant difference on the incidence of vomiting between children who received single dose prednisone 2 mg/kg/day (n=10/66) and nebulised dexamethasone 1.5 mg/kg (n=0/62), however the confidence interval was very wide that included a high number of NNTH (if we treat more than 50 children with prednisone, then we will expect one additional event of vomiting) [OR 23.23 (95% CI 1.33 to 405.54; p-value=0.03; NNH=7)] [33].

Regarding behavioural changes, one RCT [34] randomly allocated children aged two to 16 years with acute exacerbation of mild persistent asthma to receive either oral prednisone/prednisolone high dose (2 mg/kg/day) or low dose (1 mg/kg/day) for five days. There were significant differences in observed adverse events between high-dose and low-dose groups in regard to anxiety (9/43 vs 2/43, respectively) [OR 5.43 (95% CI 1.10 to 26.83; p-value=0.04; NNTH=7)] and aggressive behaviour (9/43 vs 0/43) [OR 23.96 (95% CI 1.35 to 426.33; p-value=0.03; NNTH=5)]. The wide of intervals demonstrated a wide variance in the number of children needed to treat to expect one additional adverse event. There were no significant differences in other unfavourable effects (i.e. facial fullness and erythema, abdominal pain, diarrhea, euphoria, depression, and hyperactive) [34]. Another RCT [35] included children aged two to 15 years with acute exacerbation of asthma who were randomly allocated to receive oral prednisolone 1 mg/kg/day for three days (5-day group) vs same dose of prednisolone for three days (3-day group). There were no significant differences in regard to the incidence of rash and behavioural disturbance (e.g. angriness, aggressiveness, crankiness, irritability) between the two groups [35].

An RCT of the use of prednisolone for pediatric AOM reported no significant differences between children who received oral prednisolone 2 mg/kg/day for five days and placebo group who experienced moderate side effects (e.g. drowsiness, nervousness, diaper rash, dry mouth) [18]. This study also demonstrated that there was no correlation between the use of corticosteroid and the persistence or the emergence of viral infections [18]. Other potential side effects correlated with the use of corticosteroids are fluid retention and headache [18,30].

Based on these trials, we consider 5-day duration of prednisolone for this study is appropriate and safe for children.

Clinical trial of corticosteroids for acute otitis media in children

Evidence has demonstrated insufficient benefits and harms of corticosteroids. An RCT demonstrated that corticosteroid reduced the duration of ear discharge in AOM children with ventilation tubes [26]. Another RCT demonstrated a temporary resolution of middle ear effusion after five days of corticosteroid treatment [18]. In a systematic review of randomised placebo-controlled trials (RCTs) of steroids for AOM, only two small trials [18,27,36] (very low to low quality) indicated corticosteroids could be useful in this condition. However, our confidence in the results is low, due to small sample size and very wide confidence intervals around the observed results. This insufficient evidence creates a research gap in the management of AOM, particularly in non-severe cases, where antibiotics are not required. Therefore, we propose an adequately powered clinical trial to address this uncertainty.

We will conduct a large, parallel, pragmatic, multicentre, stratified, double-blind, randomised, placebo-controlled trial with the allocation ratio 1:1 to test the effectiveness of corticosteroids for 760 children with AOM including 60 children for a tympanometric mechanistic sub-study and pilot study, described further in this protocol. As a comparator to prednisolone, we will use a placebo for the following advantages: (1) it is the most accurate test in assessing the efficacy of a treatment; (2) it will show the true additional benefits and/or harms of the prednisolone; and (3) it is crucial when the outcome is assessed using subjective measurements. The primary objective and outcome of this proposed trial is to assess the effectiveness of corticosteroids as a monotherapy in children with mild AOM, and as an addition to antibiotics in children with severe AOM, on ear pain at three days after randomisation using visual analogue scale (VAS). The secondary outcomes include ear pain at other time points, total duration and severity of pain, adverse effects, complications of AOM (e.g. perforation of tympanic membrane, mastoiditis), and AOM recurrence.

1.1.3 Rationale for pilot study

Prior to our main study, we will conduct a pilot study, described in this protocol. This study will mimic the main study in terms of its process and procedures, but on a smaller scale. However, due to budget constraints, we will conduct a pilot study as a pragmatic, randomised, open-label, single-blind study. We will blind outcome assessors (i.e. physicians and tympanometry technicians), so they will not aware of the allocation of the intervention.

The main study will involve many participating physicians and healthcare facilities across Jakarta, Bekasi, and Depok, most of whom have not been involved in a clinical trial before, will have a long follow-up period up to three months, and will utilise a symptom diary and a specific translated instrument to assess the severity of symptoms (acute otitis media – severity of symptom scale or AOM-SOS) which is not widely recognised by physicians in Indonesia. Therefore, this pilot study is crucial to test the feasibility of the main study, including the characteristics of our main study design, all the study processes and procedures (e.g. the recruitment, stratification, randomisation, outcome measurement), and other operational strategies in our proposed main study.

1.2 Objectives

The first objective of our pilot study is to assess the overall process and procedures of the main study, as follows: (1) the recruitment criteria; (2) stratification and randomisation processes; (3) outcome measures using validated and customised tools (e.g. visual analogue scale/VAS, Acute Otitis Media – Severity of Symptoms Scale/AOM-SOS, case report forms/CRFs, symptom diary); (4) identification of any potential practical and operational issues that may appear in the main study which will require re-structuration of the planned methods and procedures after commencing this pilot study; and (5) verification of sample size calculation for main study.

Our second objective is to conduct a mechanistic explanatory study using tympanometry. It aims to assess the efficacy of corticosteroids in improving the resolution of middle ear effusion in AOM.

CHAPTER 2 – METHODS

2.1 Trial design

This study is a pilot of a parallel, pragmatic, stratified, randomised, open-label, single-blind controlled trial of corticosteroids, as monotherapy for mild AOM, and in addition to individually prescribed antibiotics for severe AOM. In the main study, we will stratify eligible children based on the clinical specialty (primary care or secondary/tertiary care) and severity of AOM (mild or severe). However, for this pilot study, we only include ear-nose-throat-specialists (ENTs) who work at tertiary centres for the convenience of the implementation of the mechanistic sub-study as tympanometry is only available at the hospitals (tertiary centres). Therefore, we will stratify the children based on their AOM severity and then will randomly allocate to corticosteroid (prednisolone) or control (usual care without prednisolone) (Figure 1) with the allocation ratio of 1:1. Because it is a n open-label study, the parents/caregivers and an appointed nurse who will perform the randomisation will be aware of treatment allocation, whilst the clinicians and tympanometry technicians will remain unaware of the treatment.

2.2 Participants, interventions, and outcomes

2.2.1 Study setting

Prior to this study, we conducted a feasibility study to survey the current management of AOM in children in three cities in Indonesia and to identify the willingness of physicians to participate in our proposed clinical trial of corticosteroids for AOM in children. Based on clinical scenarios, there were sufficient number of physicians who would prescribe corticosteroids for AOM. There were 171 physicians from 87 primary/secondary to tertiary centres (public and private) in DKI Jakarta, Depok, and Bekasi who were willing to participate in our proposed main study. However, we will only pilot this study at seven public and private hospitals in Jakarta and Bekasi: (1) Dr Cipto Mangunkusumo Hospital; (2) Persahabatan Hospital; (3) Gatot Subroto Army Hospital; (4) Antam Medika Hospital; (5) Cempaka Putih Islamic Hospital; (6) Proklamasi ENT Hospital; and (7) Hermina Bekasi Hospital.

2.2.2 Eligibility criteria

2.2.2.1 Inclusion criteria

We will include 60 children aged six months to 12 years old with AOM, defined as current onset (48 to 72 hours) of AOM-relevant symptoms (e.g. earache, ear tugging/rubbing or irritability in non-verbal children). If it is feasible, otoscopic findings of middle ear effusion (e.g. bulged tympanic membrane, limited or absent mobility of the tympanic membrane, air fluid level, ear discharge) and acute inflammation (e.g. erythema) will confirm the diagnosis.

2.2.2.2 Exclusion criteria

We will exclude children:

1. with major and severe medical conditions (e.g. heart diseases, kidney failure)
2. who are immunocompromised (e.g. HIV, children receiving cancer treatment)
3. with congenital malformations and/or syndromes (e.g. cleft palate, Down's syndrome)
4. with ear ventilation tube(s)

5. exposed to persons with varicella (chicken pox) or active Zoster infection in the past three weeks without prior varicella immunisation or infection
6. who have high risk of strongyloidiasis infections with symptoms and signs of unexplained eosinophilia, skin reaction due to larvae penetration into the skin (e.g. inflammation, oedema, petechiae, severe pruritus), particularly on the feet regions, pulmonary (e.g. dry cough, throat irritation, dyspnoea, wheezing, haemoptysis, repeated episodes of fever and mild pneumonitis), or gastrointestinal symptoms (e.g. upper abdominal pain, diarrhea, anorexia, nausea, epigastric pain, malabsorption, and vomiting)
7. who have taken systemic (i.e. oral, injection) or topical steroids in the preceeding four weeks
8. who have taken antibiotics in the preceeding two weeks
9. who are hypersensitive to prednisolone or prednisone, or other corticosteroids

2.2.3 Interventions

Children in the mild AOM group will be randomly allocated to receive either a single dose of prednisolone tablets daily for five days as an addition to expectant observation or expectant observation alone (without prednisolone). At the baseline visit, the participating physicians will inform the parents/caregivers to closely observe the children for 48 hours without immediate antibiotic treatment.

Children in the severe AOM group will be randomly allocated to receive either a single dose of prednisolone tablets daily for five days as an addition to antibiotics according to physicians' preferences or antibiotic alone (without prednisolone). Antibiotic treatment is commonly prescribed for AOM with severe symptoms. The information regarding the antibiotics (e.g. antibiotic type, dose, duration) will be recorded in the case report forms (CRFs).

2.2.3.1 Prednisolone and control group

Prednisolone group

Prednisolone tablets will be given in the intervention groups in both mild and severe groups. It is given at a dose of 1 mg/kg to 2 mg/kg body weight, once daily for five days. The pharmacist will crush the tablets, mix them with sweeteners, and pack them in a daily paper-pack. It should be given in a single dose at 6 to 8 am in the morning to mimic the normal diurnal rhythm of cortisol production [19,20]. Participating physicians will advise the parents to give the prednisolone at about the same time each day as a daily routine for children which will also help parents to remember.

Control group

Due to budget constraints, we are not able to provide a matched placebo as prespecified for the main study. Therefore, we will not give placebo for children in the control group, either in the mild or severe group. Children in the control group of the mild AOM group will still receive expectant observation and those in the severe AOM group will receive antibiotics, and other concomitant treatment based on physicians' preferences (if necessary). The only difference between the intervention and control group is solely whether they receive prednisolone (intervention group) or not (control group).

2.2.3.2 Criteria for trial drug discontinuation or modification

When giving the prednisolone to a child, parent can mix the prednisolone powder with jelly or juice. If children vomit less than 30 minutes after having a dose of prednisolone, parents should give the same dose again. However, if they vomit again after 30 minutes, parents should not give another dose of prednisolone until the next dose on the next day. This should be noted in the symptom diary. If children keep vomiting after receiving prednisolone, parents should contact the research team. If the parents forget to give prednisolone to their children, they can give the missed dose as soon as they remember on the same day and they should also note this in the symptom diary.

If there are any adverse events and adverse drug reactions which have been assessed by research team that would require the discontinuation of drug trial and further assessment and treatment, then the treatment will be discontinued for this particular case, however follow-up will continue, where possible. This will be reported in the CRFs. Serious adverse events will be reported to Bond University's Human Research Ethics Committee (BUHREC) and the Research Committee Ethics Faculty of Medicine Universitas Indonesia (FMUI) – Dr. Cipto Mangunkusumo Hospital (CMH).

2.2.3.3 Adherence monitoring

Participating physicians will provide information regarding the administration of the prednisolone. The researcher will send a daily text-message reminder to all the parents in both prednisolone and control groups during the intervention period of five days to take the drug regularly and to complete the symptom diary daily. The text-message will also remind all the parents to visit the clinic after the 48-hour expectant observation or visit-1 (day-3), visit-2 (day-7), visit-3 (day-30), and visit-4 (day-90) for re-assessment. At each visit-1 and visit-2, the parents will return the first and second mini-booklets of symptom diary and the left-over drug to the appointed nurse (at visit-2). The nurse will then check the symptom diaries and the left-over drug for the adherence in taking intervention drugs. We will visit the patients' homes to collect the third mini booklet of symptom diary that will record the symptoms from day-7 to day-14 after the baseline visit.

2.2.3.4 Concomitant care and interventions

Physicians may give symptomatic medicine (i.e. ibuprofen, acetaminophen, decongestant, mucolytic) according to their usual practice and these will be recorded in the CRFs and symptom diary. Parents will record the use of these medicine in the symptom diary. The decision on concomitant medication will be made without knowledge of allocation to the prednisolone or control group.

2.2.4 Outcomes

2.2.4.1. The pilot study outcomes

Recruitment rate

Recruitment rate is defined as the proportion of consultations with potentially eligible children who provide their consent to be included in the study. As this is recognised as a crucial aspect of conducting a clinical trial and may cause study discontinuation due to low recruitment [37], we will assess this in our pilot study. We will identify the rates and challenges during the recruitment process and determine the best strategy for the main study to overcome these challenges and obstacles.

The success of the study procedures

The success of the study procedures includes the following: (1) obtaining informed consent from the patients and their parents; (2) the recruitment based prespecified eligibility criteria, including the use of otoscope to diagnose AOM if feasible; and (3) the stratification and randomisation process, including stratifying eligible children based on the severity and obtaining the allocation result whether the children will be allocated to the prednisolone or control group.

Ability to measure planned outcomes in the main study

We will assess the ability to measure planned outcomes in main study, which are: (1) the proportion of children with pain reduced by at least the minimum clinically important amount, at day-3 after randomisation. This will be assessed using a VAS recorded in the patient symptom diary; (2) the severity of pain and other AOM-relevant symptoms at various time points using VAS, AOM-SOS, and the symptom diary; (3) duration to AOM resolution; (4) adverse effects, defined using standard clinical trials criteria, recorded in the diary, and reported to the central office and ethics committee as required.; (5) complications of AOM (e.g. perforation of tympanic membrane(s), mastoiditis); and (6) AOM recurrence, defined as a new episode of AOM at one to three months after randomisation. We will report these narratively due to a limited sample size and insufficient formal power calculation for this pilot study to be able to detect actual effects of corticosteroids to improve clinical outcomes in AOM.

The compliance to study and study drug

The compliance to study and study drug is defined as a proportion of children who regularly take the study drug (assessed using the symptom diary and any left-over drug) and come to follow-up visits per protocol. Participants will be followed-up closely by clinicians and research staff. Children will return for a visit at day-3 after randomisation, ensuring collection of the primary outcome.

The verification of sample size calculation for main study

Based on our size calculation, we plan to enrol 760 children in the main study. We estimate that there will be 35% of the total sample of children with AOM in the severe group (i.e. children with severe symptoms, fever ≥ 39°C, children aged < 2 years with bilateral AOM, AOM with perforation of tympanic membrane). Therefore, within this pilot study, we can assess the accuracy of this assumption. Also, we will check another assumption of the sample size calculation, which was the proportion in the control group with the resolution of pain at three days, which was 42.5%.

2.2.4.2. The mechanistic or tympanometry sub-study outcomes

Primary outcomes

The change in middle ear effusion (MEE) at various time points

We will assess the change in the MEE at the following time points: baseline visit, visit-1 (day-3), visit-2 (day-7), visit-3 (day-30), and visit-4 (day-90). We will measure MEE using static acoustic admittance, defined as "the amount of energy absorbed by the tympanic membrane and middle ear, measured in mmho or mL" [38]. We will also measure the difference of this results between the intervention and control group.

Secondary outcomes

Duration of MEE

We will also assess the duration to the resolution of MEE using tympanometry.

The correlation between ear pain and other symptoms with the changes in MEE at various time points

We will identify the correlation between ear pain and other symptoms (i.e. ear tugging, irritability, crying, lack of sleep, lack of appetite, less of playfulness, fever) with the changes in MEE at various time points.

2.2.5 Participant timeline

Table 1 illustrates the timeline for visits and follow-ups. We will measure the outcomes at various time points: (1) visit-1 after the 48-hour observation (day-3); (2) visit-2 (day-7); (3) visit-3 (day-30); and (4) visit-4 (day-90). Patients will visit the hospital at visit-1 and visit-2, whilst the last two visits will be a home-visit. However, children in the mechanistic sub-study have to visit the hospitals at those follow-up visits. To improve the compliance of the study, the research personnel will send a daily text-message reminder to all the parents in the study during treatment period to take the drug, complete the symptom diary, and visit the clinic after the 48-hour expectant observation and other time points. At visit-2, parents will return the symptom diary and any left-over drug.

Table 1. Follow-up timeline

	STUDY PERIOD					
	Enrolment Allocation	**Post-allocation**				**Close-out**
TIMEPOINT	**0 (Day-0)**	**t1 (Day-3)**	**Intervention ends (Day-5)**	**t2* (Day-7)**	**t3* (Day-30)**	**t4* (Day-90)**
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation	X					
INTERVENTIONS:						
[Intervention A] Prednisolone (5 days)	═══	═══	═══			
[Intervention B] Control (5 days)	═══	═══	═══			
ASSESSMENTS:						
Baseline examination (weight, height, BP, body temperature)	X	X		X	X*	X*
Severity of pain and duration using VAS	X	X		X		
Overall symptoms and its duration using AOM-SOS	X	X		X		
Adherence to trial drug	X	X		X		
Adverse effects	X	X		X		
Otoscopic examination	X	X		X	X*	X*
Tympanometry examination	X⁺	X⁺		X⁺	X⁺	X⁺
Complication	X	X		X		
Recurrence of AOM					X*	X*

BP=blood pressure; VAS=visual analogue scale; AOM-SOS: acute otitis media-severity of symptoms scale

**The follow-up will be carried out by home-visit and phone, but those in the mechanistic sub-study will have their follow-up visits to the clinics; ⁺These time-point assessments will be applied only for children in the mechanistic sub-study*

Participant enrolment

In the main study, we will stratify eligible children by the clinical specialty (primary care or secondary/tertiary care) and severity of AOM (mild or severe). However, we only include ear-nose-throat-specialists (ENTs) who work at tertiary care in this pilot study. Therefore, we will stratify the children based on their AOM severity and then will randomly allocate these eligible children to receive either a single dose prednisolone for five days or without, as an addition to expectant

observation in the mild AOM group or as an addition to antibiotics according to physicians' preferences (e.g. antibiotic type, dose, duration) in the severe AOM group (see Figure 1).

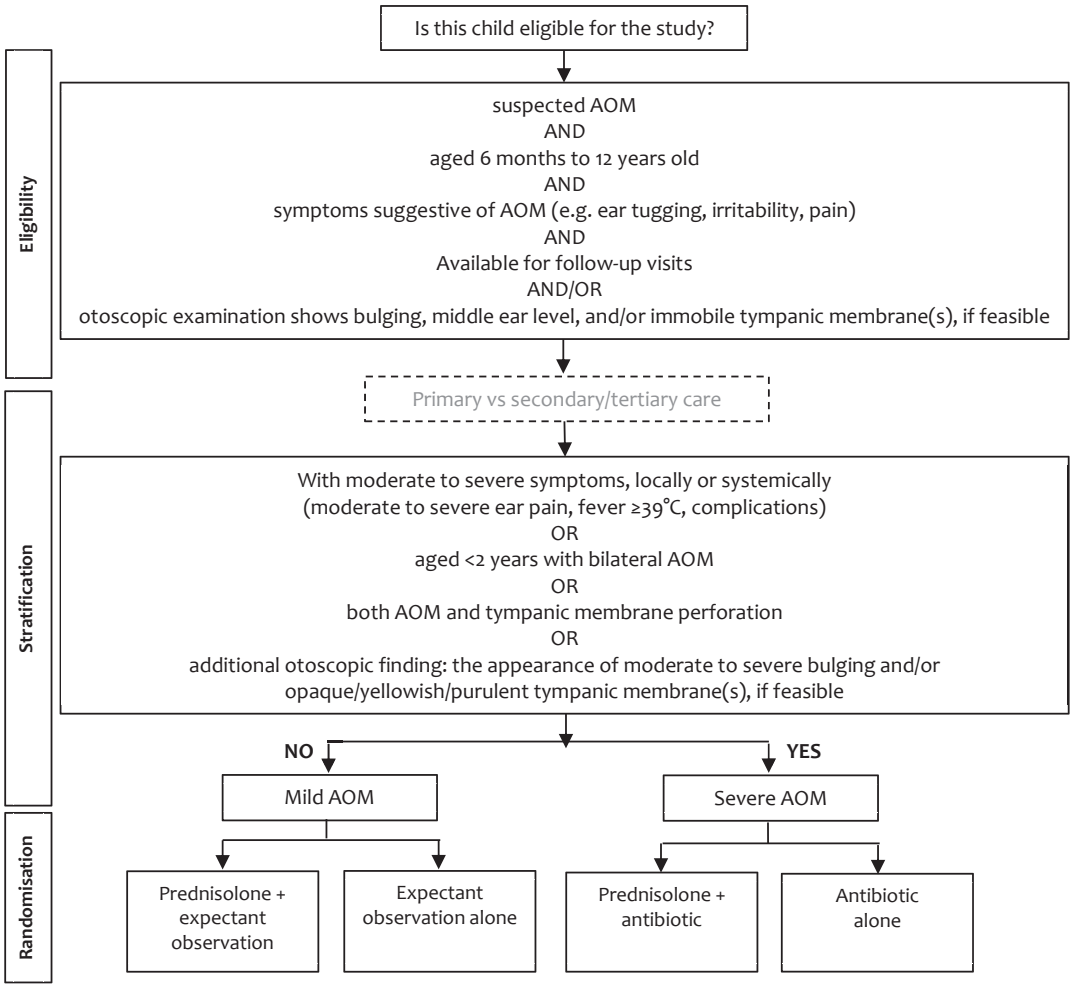


Figure 1. Flow chart of the stratification and randomization of the study

Participating physicians will assess the eligibility of children who come to the hospital based on their symptoms and clinical features of AOM. The eligible children will then be stratified based on the severity of AOM to either mild or severe AOM group. This process will be assisted using an eligibility and randomisation form. The participating clinicians will then obtain a clinical history and perform a baseline examination, including general, otoscopic, and tympanometry examination. The results of these procedures will be recorded at the baseline history form and outcomes form. The tympanometry examination will be conducted by an audiologist or a tympanometry technician. The physician will assess and analyse the tympanometry findings and record the results in the outcome form. After these procedures, the children will be sent to the appointed nurse who will perform the randomisation and dispense the prescription for a study medication (prednisolone) if the patient is assigned to the intervention group.

2.1.6 Sample size

We did not determine a sample size for the pilot study. There are several suggestions in calculating the sample size for a pilot study (e.g. at least 55 participants or at least 9% of the sample size of the main study) [39]. Since we will need 60 children in the mechanistic sub-study, we will include 60 children with AOM in our pilot study. The sample size of the mechanistic study was determined based on the main primary outcome, which is the mean value of static acoustic admittance or acoustic compliance in the tympanogram. In a previous study of children with middle ear effusion (MEE) who underwent tympanometry assessment and had a history of chronic or recurrent middle ear disease [40], the response within each subject group was normally distributed with standard deviation 0.3. If the true difference in the experimental and control means is 0.3 units, we will need to study 22 experimental subjects and 22 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. With a 20% allowance for dropouts, the total sample size becomes 56 or we will include 60 children for this pilot study.

Using the worst-scenario that of 50 physicians who work at seven appointed hospitals and have approximately 97 patients with AOM per week, we estimate that only 30% of the physicians will confirm their participation and 25% of the patients will give their consents to participate in our study. We then estimate that it will require nine months to recruit 60 children with AOM in this pilot study, including the extra months for potential slow recruitment and last follow-up (three months after the baseline visit).

2.1.7 Recruitment

Recruitment of physicians

Our feasibility survey study (April–August 2016) demonstrated there were 352 physicians (general practitioners, ear-nose-throat specialists, and paediatricians) who were willing to participate in our main study and they had 705 paediatric patients with AOM in the past seven days. For our pilot study, we identified 50 physicians from the most feasible seven hospitals located in DKI Jakarta who were willing to participate in our study and had approximately 97 paediatric patients with AOM in a week.

Recruitment of participants

After physicians deliver the patient information and obtain the consent from the eligible children, they will use the eligibility and randomisation form to assist them in stratifying the children based on their AOM severity. Physicians then will complete other CRFs, as the following: baseline history form and outcome form. Physician will assist the parents to complete the symptom diary. The similarity on the forms and sequences of both outcome CRF and symptom diary will help parents to be able to fill those correctly.

2.3 Assignment of interventions

2.3.1 Allocation

Sequence generation and implementation

All children and their parents who are eligible and consented will be enrolled, and stratified based on their AOM severities or clinical features. The randomisation process will be performed by the

appointed nurse who will randomly allocate children to either prednisolone and expectant observation or control (expectant observation alone) in the mild group and either antibiotic with prednisolone or control (antibiotic alone) in the severe group. A permuted block randomisation sequence will be computer-generated by the Centre for Research in Evidence-Based Practice Bond University, Gold Coast, Australia. Random numbers will not be disclosed to the outcome assessors (i.e. participating clinicians and audiologists/tympanometry technicians), to ensure allocation concealment. Batches of intervention packages will be dispatched to participating centres from a central pharmacy facility at the Clinical Research Supporting Unit, Faculty of Medicine Universitas Indonesia (CRSU FMUI).

Allocation concealment mechanism and implementation

The information of the eligibility and stratification which is provided by the participating physicians will help the appointed nurses to obtain the information from the randomisation website, whether the children will be allocated to the prednisolone or control group, identified by the 2-digit patient ID numbers. During the consultation, the physician will prescribe study medication for every subject with the dose based on the patient age and insert the prescription in the CRF folder. The nurse who performs the randomisation will give the prescription to the subjects who are allocated to the intervention group (prednisolone group). The subject then will give the prescription to the pharmacy, where the pharmacist will prepare the prednisolone by crushing the tablets, mixing them with sweeteners, packing the prednisolone mixed powder in a daily individual paper-pack for five days, and dispense these to the subjects along with instructions for preparation. The pharmacist will record the dispensing on the form provided by the study for this purpose.

2.3.2 Blinding (masking)

In this study, the appointed nurses and the children and their parents will know the allocation of the intervention. We will ensure that the participating physicians and the audiologists/ tympanometry technicians will be blinded to the intervention allocation during the study.

Emergency unblinding

The unblinding process should be done if there are serious adverse events and limited only to that particular participating physician.

2.4 Data collection, management, and analysis

2.4.1 Data collection methods

We will assess the outcomes using CRFs, patient symptom diary, and feedback forms. The CRFs consist of eligibility-and-randomisation, baseline history, outcomes, serious adverse events (if applicable), and drug dispensing and returned forms. The outcome form will record the severity of pain and overall symptoms with their durations using VAS and AOM-SOS, as well as the resolution of AOM signs using otoscopic and tympanometry examinations (for the mechanistic study).

We will identify the recruitment rate by assessing the proportion of children who provide their consents divided by the proportion of consultations with potentially eligible children during the trial. We will use the informed consent and a study recruitment log book to record the reason(s) why children were not randomised.

We will assess the success of the study procedures using feedback forms. On the feedback form, patients and their parents and participating physicians will rate their understanding and challenges

they have during the implementation of study procedures (e.g. obtaining the randomised 2-digit patient ID numbers and their allocation of the treatment, completing the informed consent forms and CRFs) using grading scale ranged from one to five (1=very easy; 2= easy; 3=moderate/neutral; 4=difficult; 5=very difficult).

To assess the ability to measure planned outcomes in main study, we will also use a feedback form to identify the understanding, the challenges, the complexity of the outcome assessment tools utilised for this study (e.g. CRFs and patient symptom diary which includes VAS and AOM-SOS) from the perspective of the patients and their parents and the participating physicians. The CRFs and symptom diary will record the clinical history and symptoms (e.g. VAS, AOM-SOS), as well as physical examination (e.g. temperature, blood pressure, otoscopic examination if feasible). This information will be obtained from the perspectives of the patients and their parents and the clinicians.

The VAS is acknowledged as a well-established and validated scale for assessing pain [41]. It has a 100-mm horizontal scale with 'no pain' anchor at the left endpoint and 'the most severe pain' at the right endpoint of the scale. The patient will mark a vertical line along the horizontal line as the representation of their pain level. The scale will be determined by measuring the distance from the left endpoint ('no pain') to the marked line [42]. A 10-mm difference has been reported to indicate a clinically significant change [43,44]. The AOM-SOS is used to assess the severity of other AOM-relevant symptoms daily. particularly in non-verbal children. Table 2 illustrates several AOM-related symptoms described as "no", "a little", and "a lot". This scale was developed as an outcome reporting tool scoping symptom and activity limitation due to AOM in the proceeding 12 to 24 hours [45]. Shaikh et al. [45] used the mean of 4.2 points as a minimal important difference. We have translated the original English) version of AOM-SOS to Indonesian version of AOM through forward and backward translation process.

Table 2. Acute otitis media severity of symptoms scale (AOM-SOS) [45]

We are interest finding out how your child has been doing. For each question, please place a check mark in the box corresponding to your child's symptoms. Please answer all questions			
	No	A Little	A Lot
Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	☐	☐	☐
Over the past 12 h, has your child been crying more than usual?	☐	☐	☐
Over the past 12 h, has your child been more irritable or fussy than usual?	☐	☐	☐
Over the past 12 h, has your child been having more difficulty sleeping than usual?	☐	☐	☐
Over the past 12 h, has your child been less playful or active than usual?	☐	☐	☐
Over the past 12 h, has your child been eating less than usual?	☐	☐	☐

Over the past 12 h, has your child been having fever or feeling warm to touch?	☐	☐	☐

The compliance to the study and study drug will be identified by assessing the completion of CRFs and symptom diary, particularly on the attendance of patients and the parents on their scheduled follow-up visits, the completion of the trial drug based on the symptom diary and the left-over drug. We will identify the parents who have low literacy during the informed consent process. For parents who have low literacy, we will visit their home one day after the initial visit to identify a person who lives nearby (e.g. family members, neighbours) that are able to assist the parents in completing the symptom diary, daily for two weeks. If there is noone can assist them, then the research personnel will assist them in completing the symptom diary by phone. If it is not feasible, we will visit their home daily to be able to assist them.

To assess the verification of sample size calculation for main study, we will use the CRFs.

To ensure that all the outcome data can be sufficiently collected and recorded properly according to prespecified plans, we will conduct an individual/institutional training for participating physicians prior the implementation of this pilot study. The training will include following sections: (1) introduction and summary of the study; (2) introduction of international clinical practice guidelines of AOM; (3) The diagnosis of AOM using otoscope and reporting the otoscopic results; (4) the introduction and dissemination of the principles of quality methodology clinical trial (e.g. eligibility, randomisation, blinding, outcome assessment) and good clinical practice (e.g. patient consents, confidentiality, data management); (5) practical steps of eligibility assessment, stratification, and randomisation; and (6) practical steps in completing study documentation (i.e. patient informed consents, CRFs, feedback forms, patient symptom diary).

2.4.2 Data management

The integrity and completion of data will be maintained through mechanisms such as consistency checks during data entry, and cross-checks between items after data entry. All the actions and modifications to data stored in the database will be documented and retrievable for viewing. Missing data or errors will be detected before final submission to the electronic database and will be recorded in a summary along with the descriptions for each missing and/or error data. The summary will then be notified to the co-investigators in that hospital for further investigation by checking and confirming the original forms or other resources for correction or completion for those with missing and/or erroneous data. The modification to original forms will be done by research personnel at that hospital and will be documented on paper and electronic versions. It will be annotated with the date, name, and signature of the person who is responsible for making modifications.

The central data coordinator will check the validity and completeness of study data on a regular basis. All data in the central database will be protected with a regular complete back up system.

2.4.3 Statistical methods

For the recruitment rate, we report the outcome as the proportion of children in percentages (%). For the success of the study procedures and the ability to measure planned outcomes in main study, we will report the outcomes as the proportion of clinicians in percentages based on the grading

scale of their feedback reporting on prespecified outcome measure tools. For the compliance to study and study drug, we will report the outcomes as the proportion of children in percentages who attend the follow-up visits and complete the cycle of study drug.

To assess the verification of sample size calculation for main study, we will report this outcome as the proportion of children in each stratum (mild and severe AOM group) and those with pain at Day-3 after randomisation in the control group.

For the mechanistic sub-study, we will report continuous variables (i.e. the change in MEE at various time points (mean in days standard deviation), the duration of MEE) as a mean difference (MD) with 95% confidence intervals (CI) also the difference between two groups. We also will report the correlation between ear pain and other symptoms with the changes in MEE at various time points.

2.5 Monitoring

2.5.1 Data monitoring

Data monitoring committee

Since this is a short study, we do not need data monitoring committee for this pilot study. However, independent personnel from Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit, Dr Cipto Mangunkusumo Hospital (CMH) – Faculty of Medicine Universitas Indonesia (FMUI), who is not involved in this study, will assess the process and the quality of patient recruitment, data entry, and a compilation of research data in central database. Her feedback will be important to improve the implementation of our main study.

Interim analysis

Due to the small number of recruited patients to the trial and the duration of the trial will be lesser than one year, we will not perform an interim analysis.

2.5.2 Harms

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with trial drug; whereas adverse effects or adverse drug reaction, is defined as all noxious and unintended responses to a trial drug related to any dose.

At the Visit-2 (Day-3), the appointed nurse is the first person who will identify any adverse effects (AEs). These will be identified by history taking (e.g. interview) and the symptom diary. The parents will provide information in the symptom diary regarding the adverse effects and whether they seek any treatment or medical assistance to manage AEs. The nurse then will report the adverse effects to the physicians along with the information of the intervention group which the child was allocated to. This information will be provided after the physician assess and record the primary outcome (i.e. ear pain three days after the randomization) on the 'Outcome form'. This is important to keep the concealment.

Adverse events and adverse drug reaction will be collected after they sign the written consents and being enrolled in the trial. All adverse events occurring after the enrolment into the study, during the additional treatment or hospitalization due to adverse events and/or ADR will be

recorded. A subject who experiences a serious adverse event (SAE), defined as any untoward medical occurrence at any dose that may result in-patient and/or prolonged hospitalization, persistent or significant disability, medically important events, life threatening events, and death, will receive sufficient treatment and will be recorded and reported to the Research Committee Ethics FMUI – CMH and the Bond University's Human Research Ethics Committee (BUHREC). We will responsible for any additional examinations and/or treatment that are required to manage AEs.

We will not report SAE occurring after the trial discontinuation, unless there is a temporal relationship between trial drugs or other protocol procedure to the events, as well as whether the event is unexpected or unexplained given the subject's clinical course, previous medical conditions, and concomitant medications. All the SAE will be recorded in SAE form.

2.5.3 Auditing

For the main study, we will establish an audit committee from the CRSU FMUI and CEEBM Unit CMH-FMUI which is independent from the trial investigators and the funding body. However, this will not occur separately from monitoring for the pilot study. This independent committee will conduct monitoring of source paper and electronic documents in the website system, monitor the conduct of trial in multicentre sites, interviewing the investigators and coordinators, and check the storing, distribution, and the use of trial drugs. At the start of the trial, the committee will ensure that the research staff are capable in data entry and in using the website system. Observation and quality assessment of the whole trial will be ensured to be always in accordance with the protocol and International Conference Harmonization – Good Clinical Practice (ICH-GCP) standards.

2.6 Ethics and dissemination

2.6.1 Research ethics approval

This study will be conducted according to the Declaration of Helsinki and ICH-GCP guidelines. We will seek ethics approval from: (1) the Bond University's Human Research Ethics Committee (BUHREC) Bond University, Queensland, Australia; (2) the Medical Ethics Committee of the Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; (3) the Directorate-General for Politics and General Government – The Ministry of Internal Affairs Republic Indonesia; (4) the Health Agency for the Province of DKI Jakarta; and (5) local research committee at each participating hospital.

2.6.2 Protocol amendments

Any modifications to the protocol which may impact on the trial process (e.g. the modification of study objectives, study design, study population, sample sizes, the procedures, and significant administrative sectors), potential benefits and harms/safety of the patients will require a formal amendment to the protocol. This amendment will be notified and approved by the funding body and the Ethics committee prior to its implementation. Notification is also applied to the health authorities in accordance with local regulations. Minor modifications that may not impact on the trial process will also be notified and approved by the funding body and will be notified to The Ethics Committee.

2.6.3 Consent

The participating physician will provide patient information sheet and obtain informed consent from the parent(s) or legal guardian of patients, before conducting the recruitment and

randomisation process. In obtaining the consent, the investigators will inform the trial process including known and potential risks from the trial. As children are considered a vulnerable population, those aged younger than 12 years old are considered not competent to give research consent and the parent or their legal guardian will make the decision. The parent can also make decision for children aged 12 years, however there should be assent from children to participate in the research. For parents who are illiterate, we will identify the literacy level before we start the informed consent session and will ensure that the language used in the oral and written information about the trial, including the written informed consent form, should be understandable to the parents and justified to their literacy level. During the process, the participating physician will confirm the participant's understanding of the process of the trial, including the risks and benefits. For particularly crucial topics, the participating physician will ask several questions related to that topic to ensure they are well-informed and understand. Gaining informed consent will be a major topic discussed during training sessions for staff.

The person who delivers the consent (i.e. participating physician, research assistant) also will provide their signatures on the consent form, stating that they have provided information and opportunity for potential participants to understand and raise relevant questions according the trial. We will ensure that the consent process is free of coercion. As the participation into the trial is voluntary, we will emphasise their rights to withdraw from the trial at any time without any consequences, particularly on the quality of their healthcare services.

2.6.4 Confidentiality

All information related to the trial will be stored securely at the study site and the research office. All participant information will be stored in locked file cabinets in areas with limited access. All data collection, including CRFs, test results, and administrative forms will be kept confidential by only using coded IDs as identifiers and will be stored separately from all forms and records that contain names or other identifiers (e.g. informed consents forms). All databases will be secured with limited access using password-protected access systems. All counselling sessions and general to specific examinations (e.g. ear, nose, throat examination, otoscopic and tympanometry examination) will be conducted in private rooms in the participating physicians' clinics or hospital. All the involved research staffs such as physicians, nurses, and audiologists will be required to sign agreements to preserve the confidentiality of all participants.

The confidentiality of every participant will be maintained and will not be distributed externally without the written permission of the participant, except as necessary for trial monitoring by national regulatory authorities related to the medical and research safety.

2.6.5 Declaration of interests

Respati W. Ranakusuma (RWR) has nothing to disclose.
Amanda McCullough (AMC) has nothing to disclose.
Elaine M. Beller (EMB) has nothing to disclose.
Christopher Del Mar (CDM) has nothing to disclose.
Eka Dian Safitri (EDS) has nothing to disclose.
Yupitri Pitoyo (YPO)has nothing to disclose.
Widyaningsih (WID) has nothing to disclose.
Arie Sulistyowati (ARS) has nothing to disclose.

Sudigdo Sastroasmoro (SSO) has nothing to disclose.

2.6.6 Access to data

The Principal Investigator will be given access to the cleaned data sets. She will also have direct access to each sites' data sets and by request. Project data sets will be secured using password. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

2.6.7 Ancillary and post-trial care

Short-term corticosteroids are very unlikely to have harm outside those we will be measuring. However, we will responsible for the adverse effects that occurring from the trial drug during the trial (immediate) and post-trial (ancillary care) related to trial drug. The compensation will include the treatment cost relevant with the trial drug, such as the consultation visit, additional examinations, and treatment (e.g. medicine, hospitalization cost). Due to other potential concurrent treatments within the drug trial, there will be robust review and analysis process to conclude the cause of adverse events. Participating physicians will explain the procedure for the management of adverse effects of trial drug during the process of consent approval before entering the trial. We will also include this information on the patient symptom diary, including the 24-hour emergency call and list of recommended healthcare providers.

2.6.8 Dissemination policy

2.6.8.1 Trial results

Trial results, either statistically significant or non-significant, and other components of the trial (literature review, survey study, pilot study, etc.) will be reported in a journal manuscript after being distributed to all the principal investigators to be reviewed.

2.6.8.2 Authorship

The authorships and contributions of this trial will be acknowledged on the protocol, manuscript, and the report. Before the publication in medical journal or paper presentation, the principal investigators (PIs) will provide written consent of their acknowledgment and contribution in the reported trial.

- Respati W Ranakusuma contributes in: (1) designing and developing the protocol; (2) conducting the trial; and (3) interpreting and reporting the trial in the final trial report and manuscript for publication.
- Amanda McCullough contributes in: (1) the protocol development (study design and methods); (2) interpreting the results; and (3) the writing process of the final trial report and manuscript for publication.
- Elaine M Beller contributes in: (1) the protocol development (study design, methods, and statistics); (2) interpreting the results; and (3) the writing process of the final trial report and manuscript for publication.
- Chris Del Mar contributes in: (1) the protocol development (study design, methods, and statistics), and (2) the writing process of the final trial report and manuscript for publication

- Sudigdo Sastroasmoro contributes in: (1) supervising the conduct of the trial in Indonesia; (2) interpreting the result; and (3) the writing process of the final trial report and manuscript for publication.
- Eka Dian Safitri contributes in: (1) developing the mechanistic study using tympanometry; (2) providing training related to using and interpreting tympanometry to physicians, nurses, and tympanometry technicians; (3) interpreting the tympanometry findings; and (4) reviewing the final study report and manuscript for publication
- Yupitri Pitoyo contributes in: (1) recruiting secondary and tertiary healthcare centres including the physicians and nurses; (2) interpreting the tympanometry findings; and (3) reviewing the final study report and manuscript for publication
- Widyaningsih contributes in: (1) submitting a research ethics application to the Medical Research Ethics Committee in Indonesia; (2) submitting clinical trial permits to Indonesian institutions; (3) supporting the data collection and management; and (4) reviewing the final study report and manuscript for publication
- Arie Sulistyowati contributes in: (1) providing advice and expertise in terms of paediatric patients; (2) supporting the data analysis; and (3) reviewing the final study report and manuscript for publication

2.6.8.3 Reproducible research

We will make the full protocol of this study to be publicly available to maintain its transparency and reproducibility. This full protocol will include detailed information regarding the study, particularly on study design and conduct that not are commonly include in the published protocol or information description in clinical trial registry. We will register the protocol into trial registry such as the Indonesia registry web portal (https://www.ina-registry.org/) and Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/). We also will publish the results of this study in relevant medical journal as two separate papers as the following: (1) results of the pilot study and (2) results of the mechanistic sub-study. If necessary, we will include the anonymised participant-level dataset in its appendix or online. Unpublished outcomes will be reported in the full trial report that will be linked to the published study.

APPENDICES

Appendix 1. Flow chart of patient during the baseline and other visits
Appendix 2. Patient information and consent form
Appendix 3. Case report forms
Appendix 4. Study recruitment log book
Appendix 5. Patient symptom diary
Appendix 6. Product (Lupred®) information summary

REFERENCES

1. Antibiotic resistance threats in the United States. US Department of Health and Human Services: Centers for Disease Control and Prevention. 2013.
2. The World Health Organization. Global action plan on antimicrobial resistance. Geneva. 2015. ISBN 9789241509763.
3. Harris AM, Hicks LA, Qaseem A. Appropriate antibiotic use for acute respiratory tract infection in adults: Advice for high-value care from the American College of Clinicians and the Centers for Disease Control and Prevention. *Ann Intern Med*. 2016;164:425-34.
4. Pettigrew MM, Gent JF, Pyles RB, Miller AL, Nokso-Koivisto J, Chonmaitree. Viral-Bacterial Interactions and Risk of Acute Otitis Media Complicating Upper Respiratory Tract Infection. *J Clin Microbiol*. 2011;49(11):3750–5.
5. Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, et al. Viral upper respiratory tract infection and otitis media complication in young children. *Clin Infect Dis*. 2008;46(6): 815–23.
6. Umar S, Restuti RD, Suwento R, Priyono H, Mansyur M. The prevalence and risk factors of acute otitis media in children in the municipality of East Jakarta [Prevalensi dan faktor risiko otitis media akut pada anak–anak di kotamadya Jakarta Timur]. http://lib.ui.ac.id/naskahringkas/2015-09/SP-Sakina%20Umar. Published 2013. Accessed February 20, 2016.
7. Britt H, Miller GC, Henderson J, Bayram C, Valenti L, Harrison C, et al. A decade of Australian General Practice Activity 2005-06 to 2014-15. General practice series no. 39. Sydney: Sydney University Press; 2015.
8. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA et al. Clinical Practice Guideline: The diagnosis and management of acute otitis media. The American Academy of Pediatrics. *Pediatrics.* 2013;131:e964-e99.
9. Morris PS, Leach AJ. Managing otitis media: an evidence-based approach. *Aust Prescr.* 2009;32:155–9.
10. Le Saux N, Robinson JL, Canadian Paediatric Society Infectious Diseases and Immunization Committee. Management of acute otitis media in children six months of age and older. *Paediatr Child Health*. 2016;21(1):39-44.
11. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet*. 2006;368:1429-35
12. Ministry of Health Republic of Indonesia. Clinical practice guidelines for clinicians in primary healthcare centres. Jakarta: Ministry of Health Republic of Indonesia;2014. Regulatory No. 5 year 2014.
13. Costelloe C, Metcalfe C, Lovering A, Mant David, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ.* 2010;340:c2096. doi: 10.1136/bmj.c2096
14. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD000219. DOI: 10.1002/14651858.CD000219.pub4.
15. Marom T, Marchisio P, Tamir SO, Torretta S, Gavriel H, Esposito S. Complementary and alternative medicine treatment options for otitis media. *Medicine*. 2016;95(6):e2695

16. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD001727. DOI: 10.1002/14651858.CD001727.pub5.
17. Juhn SK, Jung MK, Hoffman MD, Drew BR, Preciado DA, sausen NJ, et al. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. *Clin Exp Otorhinolaryngol*. 2008;1(3):117-38.
18. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, et al. A randomised, placebo-controlled trial of the effect of antihistamine of corticosteroid treatment in acute otitis media. *J Pediatr*. 2003;143:377-85.
19. Schimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton LL, Chabner BA, et al., eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th Ed. New York: McGraw-Hill; 2011:1209-36.
20. Gupta P, Bhatia V. [Symposium on steroid therapy] Corticosteroid physiology and principles of therapy. *Indian J Pediatr*. 2008;75(10):1039-44.
21. Indonesian Pediatric Society. Juvenile rheumatoid arthritis. In: Pudjiadi AH, Hegar B, Handryastuti S, et.al, eds. Clinical guideline Indonesian Pediatric Society. 2nd edition. Jakarta; Indonesian Pediatric Society Publishing; 2011:1-4.
22. Indonesian Pediatric Society. Acute bronchial asthma. In: Pudjiadi AH, Hegar B, Handryastuti S, et.al, eds. Clinical guideline Indonesian Pediatric Society Jakarta; Indonesian Pediatric Society Publishing;.2009:269-73.
23. Indonesian Pediatric Society. Bacterial meningitis. In: Pudjiadi AH, Hegar B, Handryastuti S, et.al, eds. Clinical guideline Indonesian Pediatric Society Jakarta; Indonesian Pediatric Society Publishing; 2009:189-92.
24. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. British Thoracic Society/Scottish Intercollegiate Guidelines Network. Revised edition; 2016:107.
25. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. www.ginasthma.org. Updated 2016. Accessed September 2, 2016.
26. Ruohola A, Heikkinen T, Jero J, Puhakka T, Juvén T, Närkiö-Mäkelä M, et al. Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes. *J Pediatr*. 1999;134:459-63.
27. McCormick DP, Saeed K, Uchida T, Baldwin CD, Deskin R, Lett-Brown MA, et al. Middle ear fluid histamine and leukotriene B4 in acute otitis media: effect of antihistamine or corticosteroid treatment. *Int J Pediatr Otorhinolaryngol.* 2003;67(3):221–30.
28. Waldron CA, Thomas-Jones E, Cannings-John R, Hood K, Powell C, Roberts A, et al. Oral steroids for the resolution of otitis media with effusion (OME) in children (OSTRICH): study protocol for a randomised controlled trial. *Trials*. 2016;17:115.
29. Melhus A, Ryan AF. Expression of cytokine genes during pneumococcal and nontypeable haemophilus influenzae acute otitis media in rat. *Infection and Immunity*. 2000;68(7):4024-31.
30. Aljebab F, Choonara I, Conroy S. *Arch Dis Child* Published Online First: 3 February 2017. DOI:10.1136/archdischild-2015-309522.
31. Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med*. 2009;360(4):329-38.
32. Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics*. 1993;92(4):513-8.
33. Scarfone R J, Loiselle JM, Wiley JF II, Decker JM, Henretig FM, Joffe MD. Nebulized dexamethasone versus oral prednisone in the emergency treatment of asthmatic children. *Ann Emerg Med*. 1995;26:480-6.
34. Kayani S, Shannon DC. Adverse behavioural effects of treatment for acute exacerbation of asthma in children. A comparison of two doses of oral steroids. *Chest*. 2002;122:624-8.

35. Chang AB, Sloots TP, Petsky HL, Thearle D, Champion AA, Wheeler C, et al. A 5- versus 3-day course of oral corticosteroids for children with asthma exacerbations who are not hospitalised: a randomised controlled trial. *MJA*. 2008;189(6):306-10.
36. Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, et al. Systemic corticosteroids for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD012289. DOI:10.1002/14651858.CD012289.
37. Denhoff ER, Milliren CE, de Ferranti SD, Steltz SK, Osganian SK. Factors Associated with Clinical Research Recruitment in a Pediatric Academic Medical Center—A Web-Based Survey. PLoS ONE. 2015;10(10): e0140768. doi:10.1371/journal. pone.0140768.
38. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: Otitis media with effusion (update). *Otorlaryngology-Head and Neck Surgery*. 2016;154(1S):S1-S41.
39. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. *J Clin Epidemiol.* 2013;66:197-201.
40. Nozza RJ, Bluestone CD, Kardatzke D, Bachman R. Identification of middle ear effusion by aural acoustic admittance and otoscopy. *Ear Hear*. 1994;15:310-23.
41. Huguet A, Stinson JN, McGrath PJ. Measurement of self-reported pain intensity in children and adolescents. *J Psychosom Res*. 2010;68:329-36.
42. Cohen LL, Lemanek K, Blount RL, et al. Evidence-based assessment of paediatric pain. *J Pediatr Psychol*. 2008;33(9):939-56.
43. Von Baeyer C. Children's self-report of pain intensity: What we know, where we are headed. *Pain Res Manag*. 2009;14(1):39-45.
44. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analogue pain score for children. *Ann Emerg Med.* 2001;37(1):28-31.
45. Shaikh N, Hoberman A, Paradise JL, et al. Responsiveness and construct validity of a symptom scale for acute otitis media. *Pediatr Infect Dis J*. 2009:28(1):9–12.

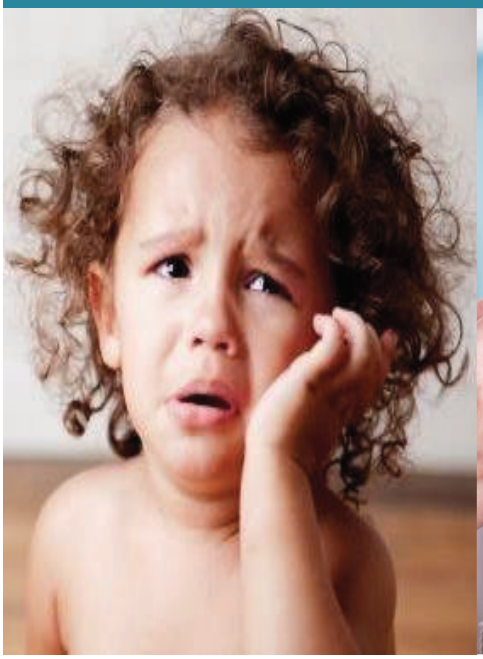
Appendix 4.2. Case report form

Case report forms (CRFs) for the pilot study were made available to readers as an additional file in the published paper. A few changes were made based on the results of the pilot. The revised CRFs are in the appendices of the next chapter (Chapter 5).

Appendix 4.3. Manual of operations

MANUAL OF OPERATIONS

Oral **P**rednisolone for **A**cute otitis media in chi**L**dren: a pilot pragmatic, randomised, open-label, single-blind study (**OPAL study**)



November 2017

Clinical Epidemiology & Evidence-Based Medicine Unit
Dr. Cipto Mangunkusumo Hospital
Faculty of Medicine Universitas Indonesia

Centre for Research in Evidence-Based Practice
Faculty of Health Sciences & Medicine
Bond University, Queensland, Australia

MANUAL OF OPERATIONS

ORAL PREDNISOLONE FOR ACUTE OTITIS MEDIA IN CHILDREN:

A PILOT PRAGMATIC, RANDOMISED, OPEN-LABEL, SINGLE-BLIND STUDY

(OPAL STUDY)

Table of Contents

Research Summary

Acute otitis media (AOM) is an inflammation of the middle ear commonly found in children with symptoms of rapid onset (less than 48 hours) of ear pain, acute inflammation, and middle ear effusion (e.g. air fluid level, bulging) [1]. AOM is often self-limiting. In general, 60% of AOM cases will have clinical symptom improvement in the first 24 hours and 80% of cases in 72 hours without antibiotic treatment [2,3]. However, antibiotics are frequently prescribed regardless of the fact they do not relieve pain symptoms in most cases [3-5]. We conducted a survey study using clinical scenarios that demonstrated up to 88% of 352 physicians in Jakarta, Depok, and Bekasi (Indonesia) would prescribe antibiotics for mild AOM. However evidence shows that only one-third of cases benefit from antibiotics, generally the more severe cases, such as AOM with moderate-to-severe local or systemic symptoms, young children (< 2 years) with bilateral AOM, and AOM with tympanic membrane perforation [6]. In addition, frequent use of antibiotics leads to increased risk of unfavourable side effects (e.g. diarrhea, vomiting, rash) and antibiotic resistance, a serious threat to health globally [3,7].

Proposed alternatives or additions to antibiotics include various herbal preparations, decongestants, and corticosteroids [8,9]. However, the evidence for these is too weak to recommend for clinical practice. The anti-inflammatory effect of corticosteroids suggests it could be a viable treatment alternative for AOM. Our survey study demonstrated that 44% of ENT specialists would prescribe corticosteroids for children with AOM. We also conducted a systematic review of randomised placebo-controlled trials (RCTs) of steroids for AOM. Although only two small trials [10-12], indicated corticosteroids could be useful in this condition, our confidence in the results is low, due to small sample size and very low to low quality evidence. Therefore, we propose an adequately powered parallel, double-blind, stratified, randomised, placebo-controlled pragmatic trial of corticosteroids for acute otitis media in children (OPAL study), to address this uncertainty.

Prior to this, we will conduct a pilot study. This study will mimic the main study in terms of its process and procedures, but on a smaller scale. However, due to budget constraints, we will conduct a pilot study as a pragmatic, randomised, open-label, single-blind study, without using a placebo. The objectives of our pilot study are to: (1) assess the overall process and procedures of the main study; (2) verify a sample size calculation for main study; and (3) conduct a mechanistic explanatory study using tympanometry. We will include 60 children with AOM, who then, based on their AOM severity, will be stratified as mild or severe AOM, and randomly allocated to an intervention group (prednisolone) or control group (without prednisolone). An appointed nurse who performs the randomisation, patient, as well as the parents will be aware of treatment allocation, however both physicians and audiologists will remain unaware of the allocation at least until the data collection at Day-3. We will assess the following outcomes: (1) recruitment rate: (2) the success of the study procedures; (3) ability to measure planned outcomes in the main study; (4) the compliance to study and study drug; and (5) the verification of sample size calculation for main study. In the mechanistic study using tympanometry, we will assess: (1) the change in middle ear effusion at various time points; (2) the duration of middle ear effusion; and (3) the correlation between ear pain and other symptoms with the changes in middle ear effusion at various time points.

If corticosteroids prove effective in relieving pain or other relevant symptoms in children, and are safe, they could become a useful alternative to antibiotics in mild cases of AOM, and an addition to antibiotics in severe cases. The treatment is relatively cheap, easy to dispense and administer. It can

also reduce antibiotic use, particularly in mild cases of AOM. This could lead to a reduction in antibiotic resistance, thus saving precious antibiotics for severe diseases where rapid response to antibiotics is critical.

References

1. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA et al. Clinical Practice Guideline: The diagnosis and management of acute otitis media. The American Academy of Pediatrics. Pediatrics. 2013;131:e964-e99.
2. Morris PS, Leach AM. Managing otitis media: an evidence-based approach. Aust Prescr. 2009;32:155-9.
3. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD000219. DOI: 10.1002/14651858.CD000219.pub4.
4. Pettigrew MM, Gent JF, Pyles RB, Miller AL, Nokso-Koivisto J, Chonmaitree. Viral-Bacterial Interactions and Risk of Acute Otitis Media Complicating Upper Respiratory Tract Infection. J Clin Microbiol. 2011;49(11):3750–5.
5. Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, et al. Viral upper respiratory tract infection and otitis media complication in young children. Clin Infect Dis. 2008;46(6): 815–23.
6. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368:1429-35
7. Costelloe C, Metcalfe C, Lovering A, Mant David, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010;340:c2096. doi: 10.1136/bmj.c2096
8. Marom T, Marchisio P, Tamir SO, Torretta S, Gavriel H, Esposito S. Complementary and alternative medicine treatment options for otitis media. Medicine. 2016;95(6):e2695
9. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD001727. DOI: 10.1002/14651858.CD001727.pub5.
10. Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB. Systemic corticosteroids for acute otitis media in children. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012289. DOI: 10.1002/14651858.CD012289.pub2
11. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, et al. A randomised, placebo-controlled trial of the effect of antihistamine of corticosteroid treatment in acute otitis media. *J Pediatr*. 2003;143:377-85.
12. McCormick DP, Saeed K, Uchida T, Baldwin CD, Deskin R, Lett-Brown MA, et al. Middle ear fluid histamine and leukotriene B4 in acute otitis media: effect of antihistamine or corticosteroid treatment. *Int J Pediatr Otorhinolaryngol.* 2003;67(3):221–30.

The Protocol

See **Appendix 1. Protocol of Oral Prednisolone for Acute otitis media in chiLdren: a pilot pragmatic, randomised, open-label, single-blind controlled study (OPAL study).**

Case Report Forms (CRFs)

To see **CRF01** to **CRF11** and **FORM01** to **FORM10**, please refer to **Appendix 2. Case report forms**.

Setting Up The Study Site

Prior to the trial, the research team will set up the site for the trial. We will provide a starting kit along with an inventory checklist. The appointed nurse who works at the site will receive the starting kit. The starting kit contains:

1. Office stationery set (e.g. pen, highlighters, scissor, glue stick, stapler)
2. File binders:
    a. Confidential study document binder:
        i. FORM01: Study registration log book
        ii. CRF01: Completed consent form
        iii. CRF02: Completed study registration form
        iv. CRF08: Completed randomisation form
    b. Case report form binder:
        i. CRF01: Participant information sheet and consent form (will be separated to confidential study binder at the end of the initial visit)
        ii. CRF02: Study registration form (will be separated to confidential study binder at the end of the initial visit)
        iii. CRF03: Eligibility form
        iv. CRF04: Baseline information form
        v. CRF05: Outcome form
        vi. CRF06: Symptom diary
        vii. CRF07: Prescription of study medication
        viii. CRF08: Randomisation form (will be separated to confidential study binder at the end of the initial visit)
        ix. CRF09: Follow-up visit card
        x. CRF10: Serious adverse event reporting form
        xi. CRF11: Feedback form
        xii. FORM07: Guideline of antibiotics for acute otitis media in children
        xiii. FORM08: Prednisolone dose for OPAL study
        xiv. FORM09: Instruction of prednisolone use for parents
        xv. FORM10: Lupred pharmaceutical brochure
    c. Study medication storage binder for the pharmacists:
        i. FORM02: Study medication stock form
        ii. FORM03: Study medication dispensing form
    d. Completed case report form and non-participating subject binder:
        i. FORM05: Recapitulation of completed case report form
        ii. FORM06: Recapitulation of non-participating subject form (e.g. not-eligible, not-consented individual forms)
    e. Study medication return binder:
        i. FORM04: Study medication return form
3. Medicine in a transparent storage container:
    a. Prednisolone tablets (Lupred® 5)
    b. Sirplus, a sweetener syrup
    c. FORM10: Pharmaceutical Lupred brochure

4. Study souvenirs:
    a. Initial visit (Day-0): Lunch box
    b. Visit-1 (Day-3): Water bottle
    c. Visit-2 (Day-7): Toys
    d. Visit-3 (Day-30): Mini towel
    e. Visit-4 (Day-90): Bag
5. Transportation cost reimbursement @$15
6. Inventory checklist form

The research team will visit and monitor the study sites at the end of the first week to check the completeness of study documentation (e.g. study document binders, case report forms), study medication stock and other supporting tools. The next monitoring visit will be conducted once every one or two weeks, depending on the recruitment flow of each site.

Study medication delivery and storage

A research member will visit the site once every one or two weeks to deliver the study medication. When receiving the study medication, the pharmacist will record the quantity, the batch number of study medication, and the date of medicines received on **FORM02: Study medication stock form** (see Appendix 2).

The study medication will be stored at the pharmacy, in a cool dry place, protected from direct sunlight, where the temperature stays below 30°C, separately from other medication. We will provide **FORM10: Lupred pharmaceutical brochure.** The pharmacist will provide the brochure to the parents, along with the study medication and the instruction of its use.

Rooms and other equipment for the study

In order to conduct the trial, we need several rooms and equipment which will be used for various activities, as follows:

1. Rooms:
    a. Nurse station:
        i. Identify the symptoms of acute otitis media using **FORM01: Study recruitment log boo**k.
        ii. Performing a general examination to measure body weight, height, temperature, and blood pressure.
    b. Consultation room:
        i. Delivering the information regarding the trial and obtain consent from the parents using **CRF01: Participant information sheet and consent form.**
        ii. Identifying the eligibility for the study and stratify the eligible children based on the severity of acute otitis media using **CRF03: Eligibility form.**
        iii. Obtaining baseline history information usimg **CRF04: Baseline information form**.
        iv. Identifying symptoms and signs of acute otitis media, including the severity of symptoms (using VAS and AOM-SOS), complication of acute

otitis media, medicine which have been taken prior the visit using **CRF05: Outcome form.**

v. Assessing the condition of nose, throat, as well as the ears using otoscope (if feasible)

vi. Explaining and tutor the parents in completing **CRF06: Symptom diary.**

vii. Assessing, interpreting, and recording the tympanometry results into **CRF05: Outcome form.**

viii. Preparing the **CRF07: Prescription of study medication** (see Appendix 10) for every study participant with doses according to their ages. The guideline for prednisolone dose is available in **FORM08: Prednisolone dose for OPAL study** and at the top of **CRF07. Prescription of study medication**

ix. Prescribing other medications, such as antibiotics for children with severe AOM based on physician's clinical preference or based on **FORM07: Guideline of antibiotics for AOM in children** and symptomatic medications, if necessary

c. Audiology room/corner:

i. Conducting a tympanometry examination.

d. Private room for randomisation process:

i. Performing and recording the randomisation of intervention allocation using **CRF08: Randomisation form**

ii. Dispensing the prescription of study medication for study participants who are allocated to intervention (prednisolone) group.

iii. Reconfirming the parent's understanding and ability in completing **CRF06: Symptom diary**

iv. Educating the parents on the use of prednisolone, identification of potential side effects, and provide the information regarding 24-hour emergency call centre. The nurse will provide **FORM09: Instructions of prednisolone use for parents**

v. Requesting the parent to complete **CRF02: Study registration**

vi. Completing **CRF09: Follow-up visit card** with scheduled visits in the next three months

vii. Providing the study souvenir and transport cost reimbursement to each study participant

viii. Collecting and checking all the study documents, storing them according their binder, and secure the binders in a locked filing cabinet:

1. The confidential study document binder (compilation with other study participant documents):
   a. FORM01: Study registration log book.
   b. CRF01: Completed consent form
   c. CRF02: Completed study registration form.
   c. CRF08: Completed randomisation form.
2. The case report form binder (no name on each form and only identified by an ID registration):
   a. CRF03: Eligibility form

b. CRF04: Baseline history form
c. CRF05: Outcome form
e. CRF10: Serious adverse events reporting form
f. CRF11: Feedback form

2. Equipment:
    a. Weight scale
    b. Measuring tape
    c. Thermometer
    d. Paediatric tensimeter
    e. Head lamp
    f. Tongue depressor
    g. Rhinoscope
    h. Otoscope
    i. Tympanometry
    j. Copy machine/scanner
    k. Office stationery
    l. Smart phone with internet connection
    m. Telephone
    n. Filing cabinet

Step-by-step Procedure

The nurse station

Objective(s)

1. Initially identify of children with acute otitis media
2. Perform general examination (weight, height, body temperature, blood pressure)
3. Provide **CRF01: Participant information sheet and consent form** and **CRF02. Study registration form** for the parents
4. Prepare the study binders and case report forms

Tool(s)

1. Weight scale
2. Height measurement
3. Thermometer
4. Paediatric tensimeter
5. FORM01. Study recruitment log book
6. Case report form binder
7. Registration ID labels
8. OPAL study stickers

Personnel

1. Attending nurse.

Procedures

1. When the medical record arrives, the attending nurse will identify whether the patient has AOM symptoms using three screening questions in **FORM01: Study recruitment log book** (see Figure 1), as follows:
    a. Has your child experienced ear pain in the past 48 hours?
    b. Has your child been tugging or rubbing her/his ear(s) and been more irritable or fussy or crying more than usual over the past 48 hours?
    c. Has your child been experiencing ear discharge in the past 48 hours?

FORM01 – STUDY RECRUITMENT LOG BOOK														
Nurse name/ID :				Study title : Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, single-blind, controlled study (OPAL study)							Hospital ID :			
Study registration ID	Patient's name	Date screened	Has your child experien-cing ear pain in the past 48 hours? (YES or NO)	Has your child been tugging or rubbing her/his ear(s) and been more irritable or fussy or crying more than usual over the past 48 hours (YES or NO)	Has your child been experie ncing ear discharg e in the past 48 hours? (YES or NO)	Body weight (kg)	Body height (cm)	Body tempe-rature (°C)	Blood pressure (mmHg)	Did patient go on the study? (YES or NO)	If YES, what is the Randomisation ID	If NO, please tell us reason not on the study below		
												Not eligible (YES or NO)	Did not give consent (YES or NO)	Was not approached (YES or NO). Write the reason

Figure 1. FORM01: Study recruitment log book.

2. If the parent responds **'YES' to one of these three questions**, the attending nurse will then perform general examination (i.e. body weight and height, temperature, blood pressure) and record the results on **FORM01. Study recruitment log book**. The nurse will also prepare the case report forms which are compiled in one binder (case report form binder), as follows:
    a. CRF01: Participant information sheet and consent form.
    b. CRF02: Study registration form
    c. CRF03: Eligibility form.
    c. CRF04: Baseline information form.
    d. CRF05: Outcomes form.
    e. CRF06: Symptom diary.
    f. CRF07: Study medication prescription.
    g. CRF08: Randomisation form
    h. CRF09: Follow-up visit card
    l. CRF10: Serious adverse events reporting form
    m. CRF11: Feedback form
    m. FORM07: Guideline of antibiotics for acute otitis media in children
    i. FORM08: Prednisolone dose for OPAL study
    i. FORM09: Instruction of prednisolone use for parents
    j. FORM10: Lupred pharmaceutical brochure
3. If possible, the nurse will provide **CRF01: Participant information sheet and consent form** and **CRF02: Study registration form** for the parents so they can read the information sheet and complete the registration form while they are waiting for consultation.
4. The nurse will then report this patient to a physician as a potential study participant along with **FORM01: Study recruitment log book** and **the case report form binder** with a specific registration ID label attached on every form in the binder. The form and binder will be inserted in the medical record of that particular patient. Therefore, the physician will notify this patient as a potential study participant for OPAL study

The consultation room

Study consent, recruitment, and stratification

Objective(s)

1. Identify the eligibility of potential children to be included in the trial
2. Provide sufficient information regarding the research, including the overall process and potential effects caused by the study
3. Obtain the consent from eligible patients and their parents to participate or not to participate in the study
4. Stratify the eligible patients based on their AOM severities

Tool(s)

1. FORM01: Study recruitment log book
2. Case report form binder:
    a. CRF01: Participant information sheet and consent form
    b. CRF02: Study registration form
    c. CRF03: Eligibility form

3. Non-participating subject form binder:
    a. FORM06: Recapitulation form of non-participating subject form.

Personnel

1. Participating clinicians

Procedures

1. The attending nurse will notify the physician that the patient has AOM symptoms and provide the physician with **FORM01: Study recruitment log book** and **Case report form binder**.
2. The physician will re-confirm the eligibility of the patient using inclusion and exclusion criteria on the **CRF03: Eligibility form** (see Appendix 1. Protocol, section 'Eligibility criteria', page 15-16). If the parent has responded **'YES' to all inclusion criteria and 'NO' to all exclusion criteria, then the patient is eligible for the study**. However, if the parent has responded at least one 'NO' to the inclusion criteria or one 'YES' to the exclusion criteria, then the patient is not eligible for the study (see Figure 2).

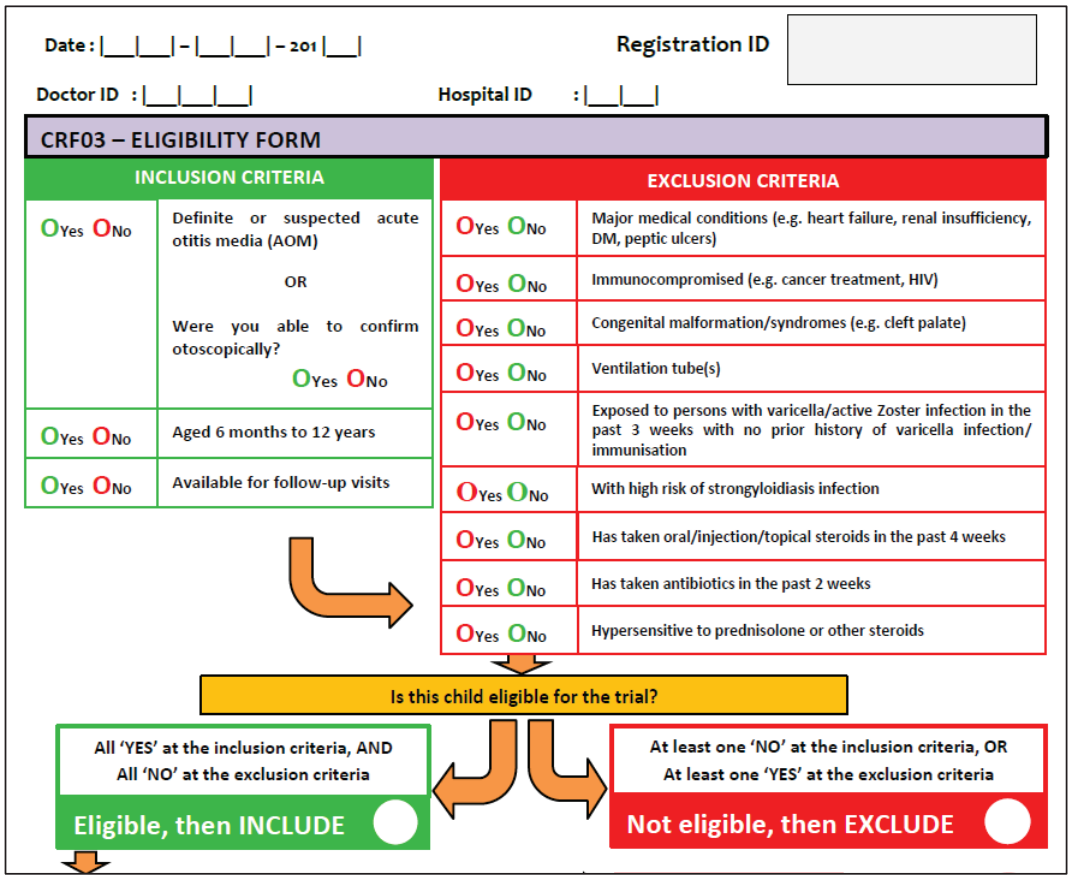


Figure 2. CRF03: The eligibility form – The inclusion and exclusion criteria.

3. After it has been confirmed that the child is eligible for the trial, then the physician will deliver the information regarding the trial and obtain the consent for the trial using **CRF01: Participant information sheet and consent form** (see Appendix.1 Protocol, section 'Consent', page 26-27). The physician will give the opportunity for the parents to

read the information sheet and raise questions, and will provide further information if necessary.

4. After the physician identifies the eligibility and obtains the consent for the study, the physician will then stratify the study participant based on the severity of the AOM symptoms according to the following criteria on **CRF03: Eligibility form** (see Appendix.1 Protocol, section 'Participant enrolment', page 19-20). :
   a. Moderate to severe symptoms, locally or systemically (e.g. moderate to severe ear pain, fever ≥ 39°C, complications)
   b. Aged <2 years with bilateral acute otitis media
   c. AOM with perforation of tympanic membrane(s)
   d. If visible, otoscopic finding shows moderate to severe bulging and/or yellowish purulent tympanic membrane(s)

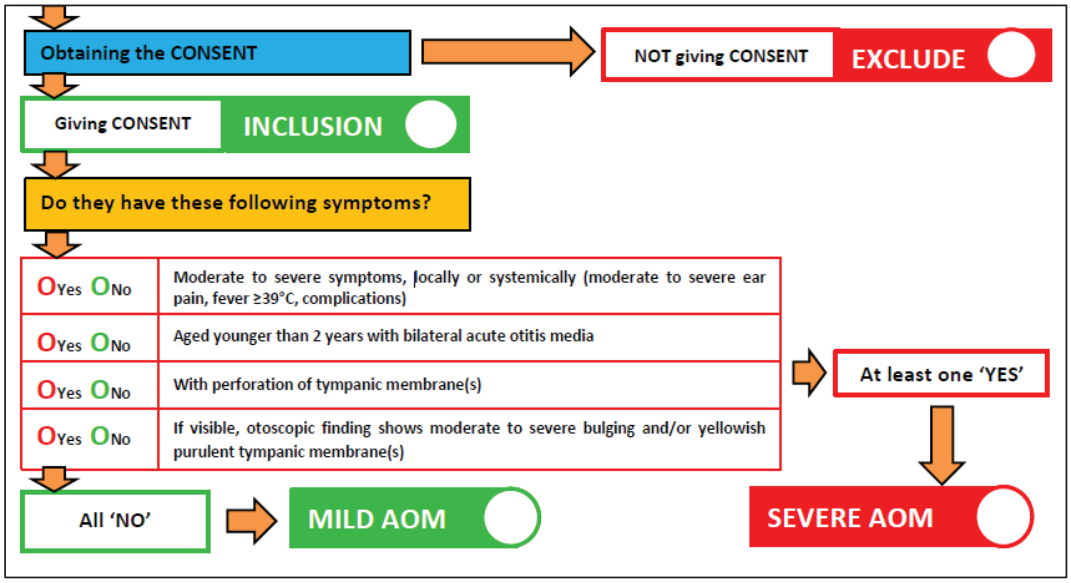


Figure 3. CRF03: The eligibility form – The consent and stratification based on severity.

5. If **the study participant has at least one 'YES' on the criteria of a to c, then the patient will be allocated to 'SEVERE AOM' group**. If the patient has **all 'NO' for a to c criteria, then the patient will be allocated to 'MILD AOM' group**. The fourth criterion (otoscopic finding) is an optional criterion because of the difficulty in identifying the tympanic membranes in small children. However, if it is visible, the physician will tick the circle corresponding to the otoscopic finding
6. For children who are stratified to 'SEVERE AOM' group, the physician will prescribe antibiotics according to their clinical preferences. However, we will provide **FORM07: Guideline of antibiotics for acute otitis media in children**.
7. The physician will then complete **FORM01: Study recruitment log book** by providing information regarding:
   a. Whether the patient participated in the study
   b. Reasons (i.e. not eligible, did not give consent, was not approached) for those who did not participate in the study
8. The nurse will complete the column 'The randomisation ID for those who went to the study' after the child has been randomised to either intervention or control group.
9. The physician will separate the case report form of children who are not eligible or do not give consent. Their eligibility forms will be removed from their case report binders and will be stored in the **Non-participating subject form binder**, after they ensure that all forms

have the registration ID label on the top right of each form. This will be recorded on **FORM06: Recapitulation of non-participating subject form.**

Collecting baseline data and examination

Objective(s)

1. Obtain relevant information to acute otitis media
2. Identify of AOM complications, severity of AOM symptoms, and history of medication
3. Perform ear, nose, and throat examination, as well as interpret the tympanometry examination result
4. Teach the parents of study participant to complete the symptom diary

Tool(s)

1. Head lamp
2. Tongue depressor
3. Rhinoscope
4. Otoscope
5. Tympanometry
6. Case report form binder:
    a. CRF04: Baseline information form
    b. CRF05: Outcomes form
    c. CRF06: Symptom diary
    d. CRF07: Study medication prescription
    e. FORM07: Guideline of antibiotics for acute otitis media in children
    f. FORM08: Prednisolone dose for OPAL study

Personnel

1. Participating physicians
2. Audiologist

Procedures

1. The physician will obtain further baseline information using the **CRF04: Baseline information form**, such as the breastfeeding history, day-care attendance, vaccination history.
2. The physician will then obtain more detailed information relevant to acute otitis media using **CRF05: Outcome form**, such as symptoms and complications of acute otitis media: ear discharge, intense pain in and behind the ear, swelling behind the ear, or facial asymmetry
3. The physician will copy the result of general examination from **FORM01: Study recruitment log book** (i.e. body weight, height, temperature, blood pressure) measured by the attending nurse.
4. The physician will identify the condition of nose and throat and record the results by ticking the circles corresponding to the findings (see Figure 4).
5. The physician will perform an otoscopic examination and record the result by ticking the circles corresponding to the findings: normal, erythema, air-fluid level, complete effusion, opacification and mild bulging, moderate to severe bulging, bulla, and/or perforation (see Figure 4 and Figure 5).

CRF05 – OUTCOME FORM					
Baseline Visit (Day-0) : |___|___| – |___|___| – 20 |___|___|					
Complications (for Physician)					
1 **Does your child experience discharge from the ear(s)?**					O Yes O No
2 **Does your child experience intense ear pain and pain behind the ear?**					O Yes O No
3 **Does your child experience swelling/bulging/ or redness/tenderness of the ear(s)?**					O Yes O No
4 **Does your child experience facial asymmetry (e.g. when the child smiles, cries)?**					O Yes O No
General and ENT examination (for Nurse and Physician)					
5.1 **Weight** ____ kg	5.2 **Height** _____ cm	5.3 **Temp.** _____ °C	5.4 **BP** ____/____ mmHg		
6 **Nose** O Normal	O Oedema	O Hyperaemic	O Livid	O Serous discharge	O Mucoid discharge
7 **Tonsils** O Normal	O Hyperaemic	O Detritus	O Tonsil(s) T1	O Tonsil(s) T2	O Tonsil(s) T3-4
8 **Pharynx** O Normal	O Hyperaemic	O Oedema	O Granules	O Post nasal drip (PND)	
9 **Otoscopic examination**					
O Normal	O Cerumen	O Erythema	O Air fluid level	O Complete effusion	O Opacification
O Mild bulging	O Moderate to severe bulging (bulging rounded)		O Bulla		O Perforation

Figure 4. CRF05: The outcome form – General, ear, nose, throat, and otoscopic

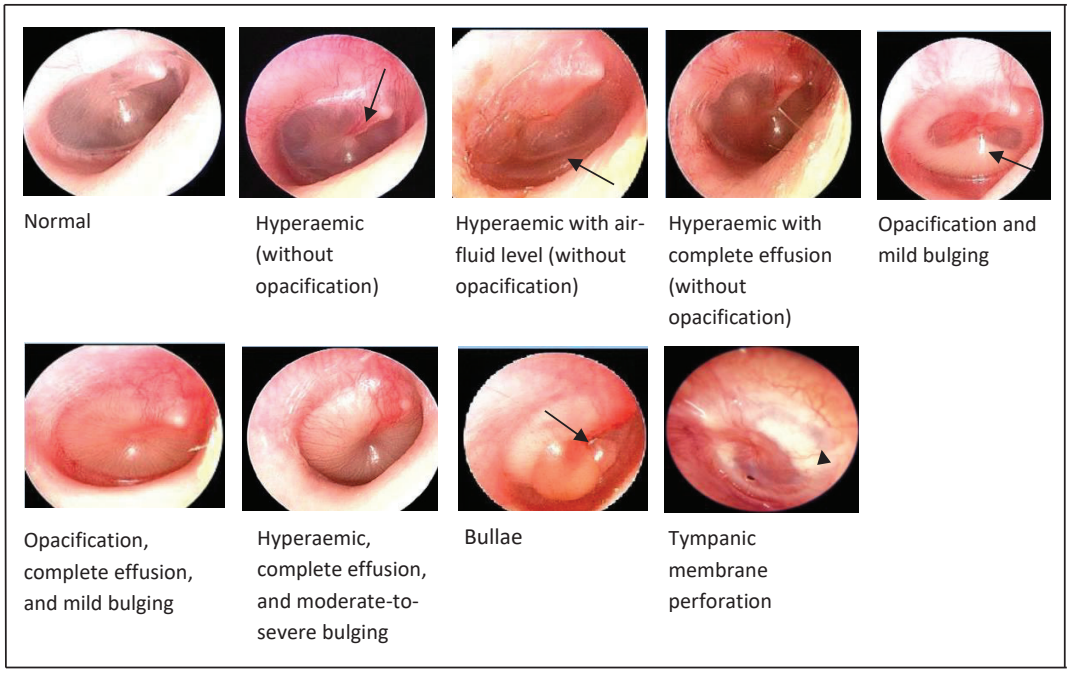


Figure 5. The otoscopic characteristics of acute otitis media.

6. The physician will then identify and record any medications that have been taken before the baseline visit prescribed by other physicians or purchased over-the-counter (e.g. antibiotics, analgesics, decongestants). The physician will also record the name and dose of medications prescribed for the study participants.
7. The physician will identify the severity of the ear pain using visual analogue scale (VAS) (see **Appendix 1. Protocol, section 'Data collection methods', page 22-23**). The VAS is a 100-mm horizontal line. The left end of the line represents 'no pain' and the right end of the line represents 'pain as bad as it could possibly be'. The physician will ask the parent to place a vertical line across the horizontal line that corresponding to the severity of ear pain during

the past 24 hours. This will also be included in **CRF06. Symptom diary**; therefore at the same time, the physician will teach the parent to complete this scale in the diary, so the parents will be able to complete this at home (see Figure 6).

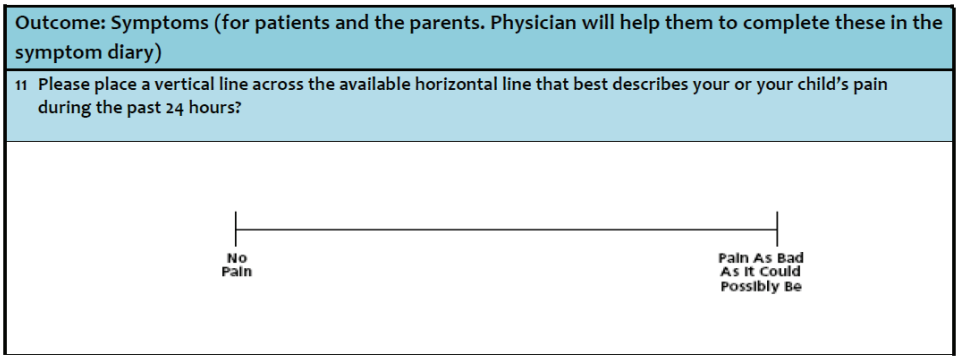


Figure 6. CRF05: Outcome form – Visual analogue scale (VAS).

8. The physician will then identify the severity of other relevant-symptoms of acute otitis media using acute otitis media severity (AOM-SOS) (see **Appendix 1. Protocol, section 'Data collection methods', page 23-24**). This consists of seven questions identifying several symptoms over the past 12 hours, as follows: has the child (1) been tugging/rubbing the ear(s)?; (2) been crying?; (3) been more irritable or fussy?; (4) been having more difficulty sleeping; (5) been less playful or active?; (6) been eating less than usual?; and (7) been having fever or feeling warm to touch?. These questions are very important for young children, particularly those who cannot express their symptoms (non-verbal children). The parent will tick the circle corresponding to the child's symptoms. This will also be included in the **CRF06: Symptom diary**; therefore, the physician will teach the parent to complete this questionnaire in the diary, so they will be able to complete this at home (see Figure 7).

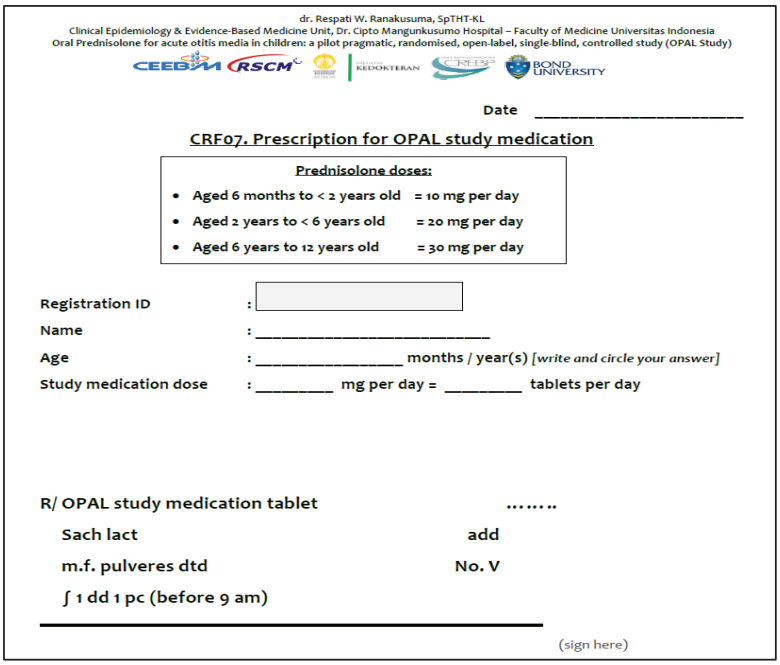
12 We are interest finding out how your child has been doing. For each question, please place a checkmark (V) in the circle corresponding to your child's symptoms. Please answer all questions.			
12.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
12.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
12.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
12.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
12.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
12.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
12.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Figure 7. CRF05: Outcome form – Acute otitis media using acute otitis media severity (AOM-SOS).

9. The physician then will provide **CRF06: Symptom diary** to the parent. The symptom diary consists of three mini booklets:
    a. The first mini booklet: The parent must complete the booklet after the baseline visit to Day-3. The appointed nurse will collect this mini booklet at Visit-1 (Day-3)
    b. The second mini booklet: The parent must complete the booklet at Day-4 to Day-7. The appointed nurse will collect this mini booklet at Visit-2 (Day-7)

c. The third mini booklet: The parent must complete the booklet at Day-8 to Day-14. The research team will collect this mini booklet at Day-14 during the home visit

10. The physician will then send the study participant to the audiology room for tympanometry examination after ensuring the ear canals are free from obstructing ear wax. Prior to this, the physician will explain the purpose and the procedure of tympanometry examination to the parents
11. After the tympanometry examination, the study participant and the parent will return to the consultation room with the tympanometry result. The physician will analyse and interpret the tympanometry findings by completing the curve type of the tympanogram.
12. Before the study participant leaves the consultation room to meet the nurse who will conduct a randomisation, the physician will prepare **CRF07: Prescription of study medication** (see Figure 8) and put it back in the **case report form binder**. The prednisolone dose can be accessed in **FORM08: Predisolone dose for OPAL study** and at the top of **CRF07: Precription of study medication**. This prescription will be dispensed by the appointed nurse to children who are allocated in the intervention group.



dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind, controlled study (OPAL Study)

Date _____

CRF07. Prescription for OPAL study medication

Prednisolone doses:

- Aged 6 months to < 2 years old = 10 mg per day
- Aged 2 years to < 6 years old = 20 mg per day
- Aged 6 years to 12 years old = 30 mg per day

Registration ID :
Name : _____
Age : _____ months / year(s) *[write and circle your answer]*
Study medication dose : _____ mg per day = _____ tablets per day

R/ OPAL study medication tablet .....
Sach lact add
m.f. pulveres dtd No. V
ʃ 1 dd 1 pc (before 9 am)

(sign here)

Figure 8. CRF07: Prescription of study medication.

13. The physician will also prescribe antibiotics for study participants with severe AOM based on the physician's clinical preference. We will provide **FORM07: Guideline of antibiotics for AOM in children** for their reference. The physician may prescribe symptomatic medication. We will ask them not to prescribe oral steroids
14. The physician will advise the parent to closely observe the study participant for 48 hours for persistence or the worsening of the symptoms (i.e. ear pain, fever) and potential complications (i.e. ear discharge, swollen on the back of the ear). If the parents identify any condition above, they should bring the study participant back to the hospital at any time for re-assessment and the initiation of antibiotic treatment
15. At the following visits (Day-3), the physician will identify any side effects such as abdominal pain, vomiting, diarrhea, anxiety. The physician will also identify whether the parent should

seek any medical help due to the side effects (e.g. go to other physicians, go the emergency department) and whether the parent should continue or stop the medication

16. The physician will record the additional medication or treatment or examination that is given due to the side effects or whether the study participant requires a hospitalisation.

Tympanometry test

Objective(s)

1. Measure the condition in the middle ear

Tool(s)

1. Tympanometer
2. Otoscope
3. Case report form binder:
    a. CRF05. Outcome form
4. Glue stick
5. Copy machine or scanner

Personnel

1. Audiologist or trained nurse

Procedures

1. The audiologist will explain the procedure of tympanometry examination
2. The audiologist will ask the parent to hold the child's head firmly. Then the audiologist will identify the condition of ear canal using an otoscope to identify any ear wax and estimate the size of the ear cuffs. After connecting the ear cuffs to a probe tip, the audiologist will slowly insert the probe tip into the ear canal until the graphs appear on the screen. This procedure will be repeated on the other side of the ear. After the graphs indicate sufficient results (e.g. no air leak, no block), the result is then ready to be printed.
3. The audiologist will document the tympanometry results on **CRF05: Outcome form – Tympanometry examination** (see Figure 9), as follows: (1) ear canal volume; (2) compliance; (3) static acoustic admittance; (4) middle ear pressure for both ears. Several tympanogram machines use terminology 'compliance' for 'statistic acoustic admittance', therefore we provide both components in this section to avoid confusion. The physician will analyse and determine the type of tympanogram curve after this examination.

13 Tympanometry examination (for Audiologist and interpreted by Physician)

O Cannot be performed. Reason: _____

Tympanogram types (will be completed by physician)	[R] Type _____	/ [L] Type _____
Ear canal vol (ECV)	[R] _____ mL	/ [L] _____ mL
Static acoustic admittance	[R] _____ mL	/ [L] _____ mL
Compliance (SC)	[R] _____ mL	/ [L] _____ mL
Middle Ear Pressure or TPP	[R] _____ daPa	/ [L] _____ daPa
Gradient or TW	[R] _____ daPa	/ [L] _____ daPa

Put the copy of tympanometry copies here

Figure 9. CRF05: Outcome form – Tympanometry examination.

4. The audiologist will attach the study registration ID label and write the date of examination on the printed tympanometry result paper, copy (using the copy machine or scanner), and attach the copied tympanometry result on the 'Tympanometry examination' section.
5. After the examination, the audiologist will send the study participant and the parent back to the consultation room. The physician then will analyse and interpret the tympanometry findings and conclude the consultation in his/her usual way.

Randomisation

Objective(s)

1. Randomly allocate the children to receive either prednisolone (intervention group) or none (control group)

Tool(s)

1. Smart phone or computer with internet connection for accessing the randomisation website
2. Telephone to call a randomisation call-centre
3. Case report form binder:
    a. CRF01: Participant information sheet and consent form
    b. CRF02: Study registration form
    c. CRF03: Eligibility form
    d. CRF06: Symptom diary
    e. CRF07: Prescription of study medication
    f. CRF08: Randomisation form
    g. CRF09: Follow-up visit card
    h. FORM08: Prednisolone dose for OPAL study
    i. FORM09: Instruction of prednisolone use for parents
    j. FORM10: Lupred pharmaceutical brochure
4. Confidential study document binder:
    a. Completed FORM01. Study recruitment log book
    b. Completed CRF01. Completed consent form
    c. Completed CRF02. Completed study registration form
    d. Completed CRF08. Completed randomisation form
5. Completed case report form and non-participating subject binder:
    a. Non-participating subject form (e.g. not-eligible, not-consented individual forms)
6. Study souvenirs
7. Transport cost reimbursement envelope

Personnel

1. Appointed nurse

Procedures

1. The appointed nurse will complete **CRF0: Randomisation form** to randomise the intervention allocation for each patient (see Figure 10). The appointed nurse requires **FORM01: Study recruitment log book; CRF01: Consent form;** and **CRF02: Eligibility form** to be able to answer several questions and confirm the answers, as follows:

a. **Part 1 – Eligibility criteria**: all 'YES' for all inclusion criteria and all 'NO' for all exclusion criteria. The nurse will check the eligibility of the study participant using **FORM01: Study recruitment log book** and **CRF03: Eligibility form**
b. **Part 2 – Consent to the study**: consent to the study has been given. The nurse will check the consent to the study using **CRF01: Consent form** and **CRF03: Eligibilty form**
c. **Part 3 – Randomisation information**: Parents' mobile numbers, the severity of AOM (The nurse will check the severity using **CRF03: Eligibilty form**), and patient's date of birth and age.
d. **Part 4 – Randomisation result**: randomisation ID, intervention allocation (prednisolone or no prednisolone / control group), and prednisolone dosage for patient who is allocated to prednisolone group. The nurse will use **FORM08: Prednisolone dose for OPAL study** as a guidance for the prednisolone dose. The dosages of prednisolone will be determined based on age, as follows:
    i. Children aged 6 months to < 2 years will receive 10 mg per day (or 2 tablets per day) for 5 days
    ii. Children aged 2 years to < 6 years will receive 20 mg per day (or 4 tablets per day) for 5 days
    iii. Children aged 6 years to 12 years will receive 30 mg per day (or 6 tablets per day) for 5 days

CRF08 – RANDOMISATION FORM									
Eligibility criteria (cross-check with 'FORM01. study registration log book', and 'CRF03. Eligibility form' in the 'Case Report Form Binder' of this subject).									
All YES for all inclusion criteria						O Yes		O No	
All NO for all exclusion criteria						O Yes		O No	
Consent to the study questions (cross-check with 'CRF01. Informed consent' in the 'Case Report Form Binder' of this subject).									
Has consent given?						O Yes		O No	
RANDOMISATION									
Father's mobile phone number									
Mother's mobile phone number									
Severity of AOM	**O Mild AOM**					**O Severe AOM**			
Subject's date of birth	Date		Month		Year		**AGE**		Month/year
RANDOMISATION RESULT									
Randomisation ID									
This subject is allocated to	**O Prednisolone group**					**O Control group (no prednisolone)**			
Prednisolone dosage (if the subject is allocated to prednisolone group)	**O 10 mg/day**			**O 20 mg/day**			**O 30 mg/day**		
Nurse's signature		Nurse's name				Date			

Figure 10. CRF08: Randomisation form.

2. The nurse will use Part 1 to Part 3 to obtain the randomisation result in Part 4 section. This can be accessed within two ways, as follows:
    a. Randomisation website:
        i. The appointed nurse will receive an invitation email from **MASCOT.org.au.** This email will notify the nurse regarding the name of the study, which is **OPAL STUDY**, and the name of institution (e.g. Cipto Mangunkusumo Hospital, etc.). Prior to the study, we obtained a list of email addresses of potential appointed nurses during the training session. For practice, we sent the invitation email from MASCOT.org.au with

the title of study of **PRACTISE STUDY**. The nurses were able to use this link to practice as much as they like until they are competent to use this tool.

ii. At the end of the email, there is a link to the **MASCOT study randomization system website** (see Figure 11).

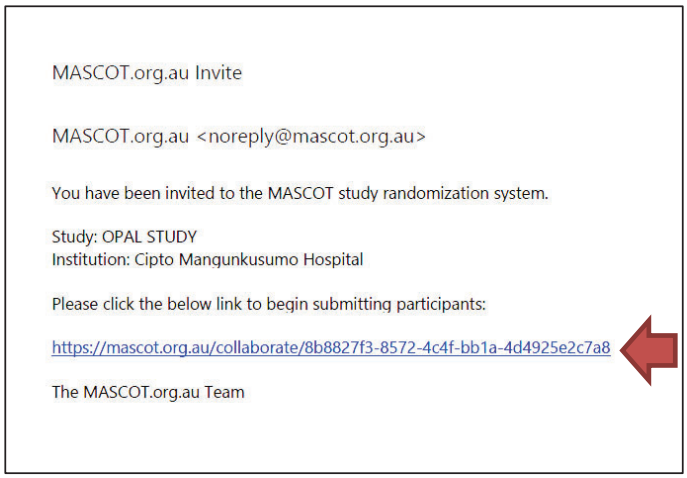


Figure 11. The MASCOT study randomization system – Invitation email for MASCOT study

iii. After clicking the link, the attending nurse will automatically open the login page of the MASCOT study randomization system website. The first page will confirm the name and institution. If the information is correct, the nurse will click **'Begin'** button (see Figure 12).

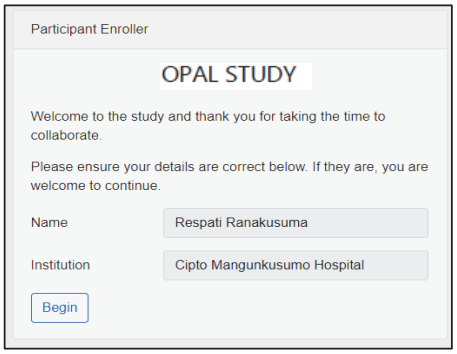


Figure 12. The MASCOT study randomization system – The enroler confirmation page.

After that, the page will ask the nurse to insert the Registration ID of the study participant (see Figure 13). The nurse will use the ID based on the Registration ID label attached on the top right of case report forms and the binder.

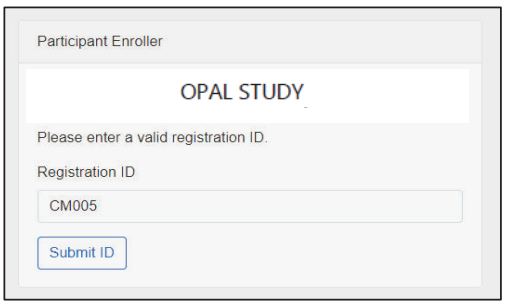


Figure 13. The MASCOT study randomization system – The study

iv. The next page presents several questions regarding the eligibility criteria (inclusion and exclusion criteria) and whether the consent the study has been given, as follows:
    1. All 'YES' for all inclusion criteria
    2. All 'NO' for all inclusion criteria
    3. Has consent been given

    The nurse will then click **'Select' → 'Yes' to all questions to be able to proceed to the next step**. To proceed, the nurse will click **'Check Eligibility'** button at the left bottom of the page (see Figure 14).

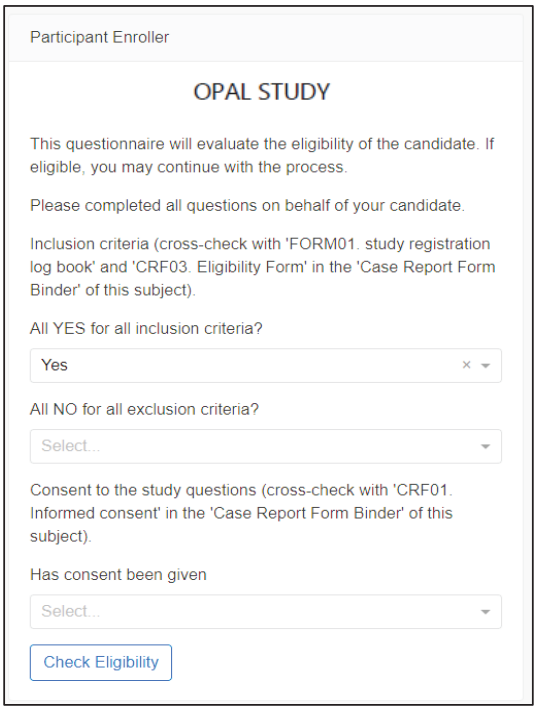


Figure 14. The MASCOT study randomization system – The eligibility page.

v. The next page will show whether the study participant is allocated to prednisolone or control (no prednisolone) group. The attending nurse will insert the date of birth using an available calendar or put the month (mm) / date (dd) / year (yyyy) manually. The nurse will check the date of birth on the available calendar. The page will automatically convert this information to age of that particular patient (please recheck the age). The nurse will select the severity of AOM based on the information in CRF03. Randomisation form, as a 'Mild AOM' or 'Severe AOM' accordingly. To proceed, the nurse will then select **'Submit Answers'** button. The nurse must ensure that the submitted answers are correct as there **will be no opportunity** to correct the answers after they have been submitted (see Figure 15).

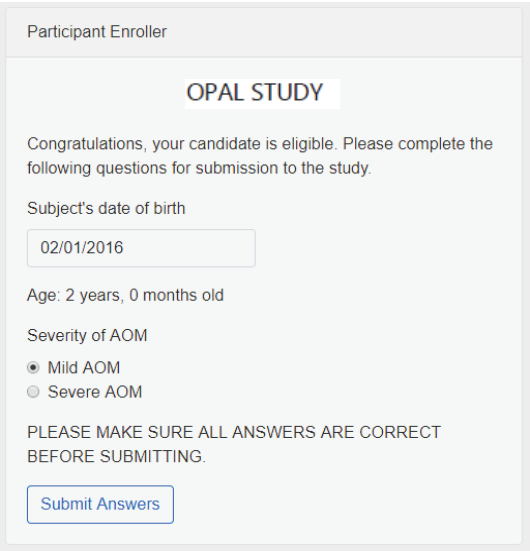


Figure 15. The MASCOT study randomization system – The date of birth and AOM severity page.

vi. If the patient is allocated to the prednisolone group, then the page will require information of the dose of prednisolone:
    1. Children aged 6 months to < 2 years will receive 10 mg per day (or 2 tablets per day) for 5 days
    2. Children aged 2 years to < 6 years will receive 20 mg per day (or 4 tablets per day) for 5 days
    3. Children aged 6 years to 12 years will receive 30 mg per day (or 6 tablets per day) for 5 days

    The nurse must ensure that the prednisolone has been prescribed according to the dose on **CRF07. Prescription of OPAL study.** This must be prepared by the physician before the randomisation process. The nurse can also check the dose using **FORM08. Prednisolone dose of OPAL study.** The nurse will then select the dose accordingly. The nurse will select **'Submit'** button (see Figure 16).

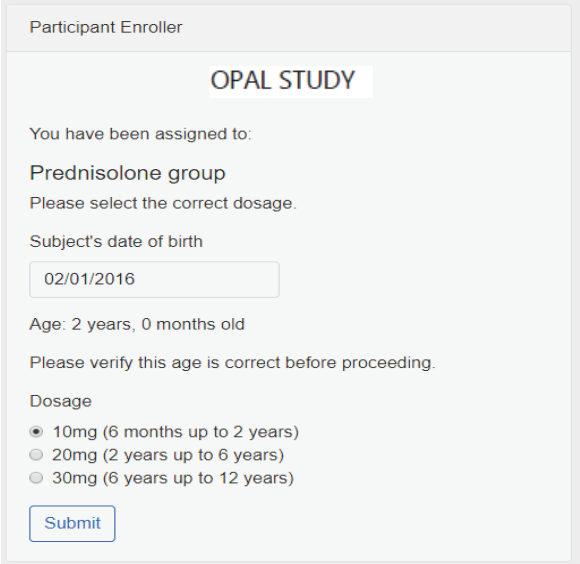


Figure 16. The MASCOT study randomization system – The prednisolone dose.

vii. The next page will provide the randomisation results (see Figure 17), as follows:
   1. **Treatment group**: the prednisolone or control (no prednisolone) group
   2. **Dosage of prednisolone** for patient who is allocated to the prednisolone group. This information will not be available for patient who was allocated to the control group.
   3. **Registration ID**. This will confirm the Registration ID that the nurse has submitted at the start of the randomisation process
   4. **Randomisation ID**. This is a new specific ID for patient that has been randomised.
   5. **Study**. This will confirm the name of the study, which is 'OPAL STUDY'.

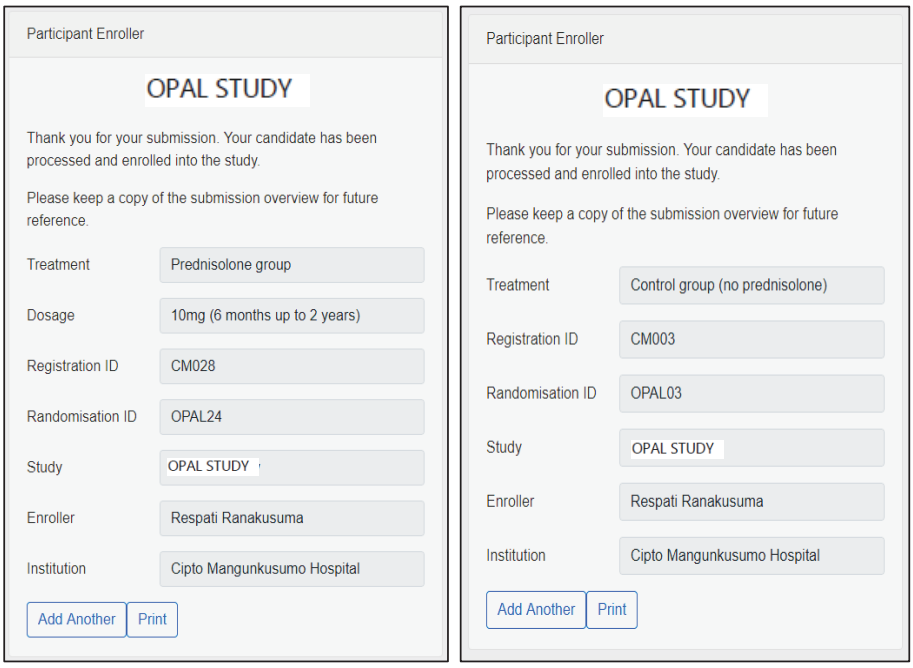


Figure 17. The MASCOT study randomization system – The randomisation result page for the prednisolone and control groups.

viii. The nurse will copy the randomisation result to **CRF08: Randomisation form.** This form will then be separated from the **case report form binder** to the **confidential study document binder**. This information will be concealed from the physicians and audiologists

ix. If the nurse is using a computer that is connected to the printer, then the nurse can directly print the randomisation result page. However, if using smart phone, then the nurse can download the page to be recalled and printed later. The nurse can click **'Add Another'** button if there is another patient to be randomised.

b. By phone:
   i. The attending nurse can contact the principal investigator (+62 8111 012 185) or the research assistant (+82 812 8799 0123) who will access the MASCOT study randomization system website.
   ii. The attending nurse has to complete **CRF08: Randomisation form** and report all information from this form to the research assistant by phone, as follows:
      1. Name of the appointed nurse and the institution
      2. Registration ID

3. All 'YES' for all inclusion criteria
4. All 'NO' for all inclusion criteria
5. Has consent been given?
6. Date of birth and age of the patient
7. Dose of the prednisolone (please confirm with **FORM08: Prednisolone dose for OPAL study** and **CRF07: Prescription of study medication**)
8. Severity of AOM

iii. The research assistant will require five minutes to access the randomisation system website and provide the randomisation allocation results back to the nurse.

iv. The research assistant will call the attending nurse and provide the information, as follows:

1. **Randomisation ID**
2. **Treatment group**: prednisolone or control (no prednisolone) group
3. **Dosage of prednisolone** for patient who is allocated to the prednisolone group. This information will not be available for patient who was allocated to the control group.

v. This information will be recorded at the bottom column of **CRF08: Randomisation form**. This form will then be separated from the **case report form binder** to the **confidential study document binder**. This information will be concealed from the physicians and audiologists.

3. For patients who are allocated to the prednisolone group, the nurse will dispense **CRF07: Prescription of study medication** to the parent(s). The nurse will provide information regarding the use of prednisolone, as follows:
   a. Taking the medication all at once, in the morning before 9 am after breakfast, everyday, for five days as
   b. Mixing the medication with sweetener syrup that has been provided by the study
   c. Mixing the medication with milk, juice, jam, or jelly, if necessary
   d. Giving back one dose of medication if the child vomits less than 30 minutes after taking the medication. However, if the child vomits after 30 minutes, then the parent should not give another dose.

   The nurse will also provide **FORM09: Instruction of prednisolone use for parents**
4. For every patient, the nurse will confirm whether the parent(s) have already had **CRF06: Symptom diary** and understood how to complete it.
5. The nurse will provide **CRF09: Follow-up visit card** for each patient. The nurse will write scheduled dates for follow-up visits, based on the initial visit.
6. The nurse will ask the parent(s) to complete **CRF02: Study registration form**, if it has not been completed.
7. The nurse will remind the parent(s) to observe the patient and come to the hospital for follow-up visit after 48 hours (day-3) or if the study participant's condition worsens at any time or does not show clinical improvement within 48 hours. The nurse will inform the parent(s) that the parent(s) can contact the 24-hour call centre for any questions or assisstances at anytime.
8. The nurse will also ensure the study participant and the parent(s) will not inform their physician and audiologist regarding the intervention they received in the trial (prednisolone or without prednisolone) until at least the outcome measurement or data collection at Day-3.

9. The nurse will give Rp. 150.000,- (approx. $15) cash for **transportation cost reimbursement** in an envelope to the parent(s).
10. The nurse will provide **study souvenirs** to the patient in each visit, as follows:
    a. Initial visit (Day-0): Lunch box
    b. First visit (Day-3): Water bottle
    c. Second visit (Day-7): Toys
    d. Third visit (Day-30): Mini towel
    e. Fourth visit (Day-90): Study bag
11. Before sending the patient home, the nurse will check the completeness of all study documents from the binders:
    a. Case report form:
        i. CRF01: Consent form
        ii. CF02: Study registration form
        iii. CRF03: Eligibility form
        iv. CRF04: Baseline information form
        v. CRF05: Outcome form
        vi. CRF08: Randomisation form
        vii. CRF10: Serious adverse events reporting form
        viii. CRF11: Feedback form
    b. Confidential study document binder:
        i. FORM01: Study recruitment log book, including copy the randomisation ID to the form, and reasons if patient has not been recruited to the study.
12. The nurse will apply a sticker on the patient medical record as an identification that the patient is in the OPAL study (see Figure 18), as well as on the page of consultation page in the medical record (see Figure 19).

Figure 18. The OPAL study identification sticker for the cover of medical record.

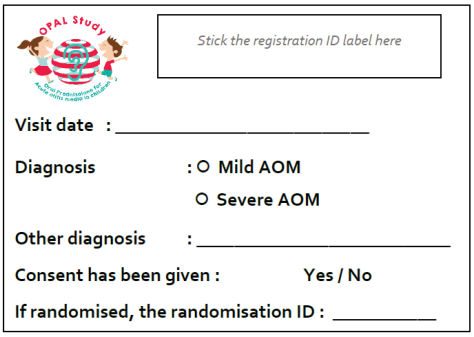


Figure 19. The OPAL study identification sticker for the medical record page.

13. When the process is over, the patient has left the room, and all documents are well completed, the nurse will then separate the forms into the binders:
    a. Case report form:
        i. CRF03. Eligibility form
        ii. CRF04. Baseline information form
        iii. CRF05. Outcome form
        iv. CRF10. Serious adverse events reporting form
        v. CRF11. Feedback form
    b. Confidential study document binder:

i. FORM01. Study recruitment log book
ii. CRF01. Consent form
iii. CRF02. Study registration form
iv. CRF08. Randomisation form

c. Completed case report form and non-participating subject binder:

i. FORM06. Non-participating subject form (e.g. not-eligible, not-consented individual forms).

14. The nurse will then secure all documents and binders in the locked cabinets.

Preparing and dispensing the study medication

Objective(s)

1. Prepare the prednisolone tablets in form of powder and the sweetener syrup
2. Dispense the study medication along with the instruction for its use
3. Record the dispensing using the **FORM03: Study medication dispensing form**

Tool(s)

1. CRF07: Prescription of study medication
2. Prednisolone tablets
3. Sweetener syrup
4. FORM03: Study medication dispensing form
5. FORM10: Lupred pharmaceutical brochure

Personnel

1. Pharmacist

Procedures

1. The pharmacist will receive **CRF07: Prescription of study medication** from the parents and prepare the study medication according to the prescribed dose. Prior to this, the pharmacist will recheck the dose using the prednisolone dose guideline attached on the top of the prescription.
2. The pharmacist will then prepare the prednisolone by crushing the prednisolone tablets, mixing them with sweeteners, and packing them in five daily paper-packs.
3. The pharmacist will dispense the study medication with the instruction, as follows:
    a. give the medicine in the morning, after breakfast and in the morning (before 9 am), everyday for five days
    b. mix the medicine with sweetener syrup of a ratio of 1:3
    c. give the medicine with a glass of water, milk, or juice, or mix it with a small amount of soft food such as jam, or yoghurt
    d. give the medication all at once
    e. if the child vomits in less than 30 minutes after taking the study medication, then the parent should give another dose.

    The pharmacist will also provide **FORM10. Lupred pharmaceutical brochure for the parents**
4. The pharmacist will complete **FORM03: Study medication dispensing form** by recording the registration ID, the study medication dose, and date dispensed for the study medication

Returning the study medication

Objective(s)

1. Identify the adherence to the study medication by collecting the left-over medication
1. Record the study medication return using **FORM04. Study medication return form**

Tool(s)

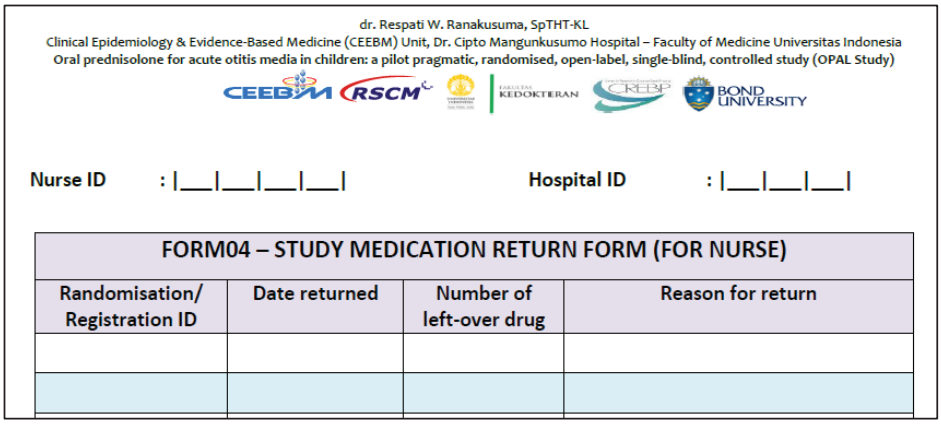
2. FORM04. Study medication return form

Personnel

1. The appointed nurse

Procedures

1. At Day-7, the appointed nurse will collect the left-over study medication, including the paper-wrap, and record this on **FORM04: Study medication return form** (see Figure 20)**.**



dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine (CEEBM) Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind, controlled study (OPAL Study)

Nurse ID : |___|___|___|___| **Hospital ID** : |___|___|___|

FORM04 – STUDY MEDICATION RETURN FORM (FOR NURSE)			
Randomisation/ Registration ID	**Date returned**	**Number of left-over drug**	**Reason for return**

Figure 20. FORM04: Study medication return form (for nurse).

Follow-up Visits

Each study participant will have additional four follow-up visits after the baseline visit (Visit-0), as follows (see **Appendix 1. Protocol, section 'Participant timeline', page 19**):

1. First visit (Visit-1) on day-3 (48 hours after the baseline visit)
2. Second visit (Visit-2) on day-7 after the completion of 5-day cycle of study medication
3. Third visit (Visit-3) on day-30 or month-1
4. Fourth visit (Visit-4) on day-90 or month-3

Using the information of parents' mobile phone numbers provided on **CRF02: Study registration form**, a research assistant will send a daily text message as a reminder: (1) to remind the parents to give the prednisolone (for study participant in the prednisolone group) every morning for five days, (2) to observe any adverse events; (3) to visit the hospital at Day-3 and Day-7, and (4) to complete the symptom diary for two weeks. For the third and fourth visits, the research coordinator will send reminder text messages one week and one day before the follow-up dates (see **Appendix 1. Protocol, section 'Adherence monitoring', page 17**).

First follow-up visit (Day–3)

The study participant and the parent(s) will have the first visit after 48 hours observation or on the third day after the baseline visit. If they miss the follow-up visit at Day-3, they can still come until the next two days (Day-4 to Day-5) after the scheduled date.

The study participant will come to the nurse station. The attending nurse will:

1. Identify the patient as a study participant by the OPAL study sticker on the front page of medical record.
2. Measure and record the weight, height, body temperature, and blood pressure
3. Report and send the study participant to the appointed nurse.

The appointed nurse will:

1. Use the registration ID label on the OPAL study sticker to find that particular **case report form binder** from the filing cabinet.
2. Check the completeness of the case report forms in the binder
3. Obtain information from the parents regarding the symptom of AOM, any complications (i.e. mastoiditis, perforation of tympanic membrane, and the adherence on the study medication use, as well as identify side effects, and complications of acute otitis media) from the first mini-booklet of the symptom diary.
4. Check the completeness and collect **the first mini booklet of CRF06: Symptom diary**. The nurse will confirm the symptoms, complication, or any side effects reported in the symptom diary. The nurse will place the **first mini booklet of symptom diary** back to the **case report form binder**. The nurse will remind the parent to continue completing the second mini booklet of symptom diary. the parent should complete the symptom diary in the next morning before administering any medicine to their children.
5. Check whether the study participant still has a sufficient number of study medication for the next two days.
6. Report the study participant to any participating physician on duty that day, along with the **case report from binder.**

7. After the study participant finish the consultation and data collection with the participating physician, the study participant again will meet the appointed nurse. The appointed nurse will check the completeness of all study documents in the **case report form binder**.
8. Record the visit date on **CRF09: Follow-up visit card**
9. Remind the parent to take the study medication regularly, complete the second mini booklet of the symptom diary, and to come for the next follow-up visit (Visit-2) at the Day 7.
10. Hand over a study souvenir (lunch box) and transport cost reimbursement envelope for each study participant.

The participating physician will:

1. Identify any complications of AOM and perform ENT, otoscopic, and tympanometry examination.
2. Identify the severity of AOM symptoms using VAS and AOM-SOS on **CRF05: Outcome form.**
3. Assess whether there is a sufficient improvement of symptoms over the past 48 hours. If there is no improvement or worsening of the symptoms of acute otitis media, based on the clinical judgement, the physician may prescribe antibiotics for the study participant in the mild AOM group or change the antibiotics for the study participant in the severe group. This will be recorded in **CRF05: Outcome form.**
4. Identify any side effects. If it is necessary to determine the treatment for the side effects, the physician can retrieve the information from the nurse whether the study participant was allocated to prednisolone or control group. However, this must be done after the physician complete assessing and recording all outcome data in **CRF05: Outcome form.**
5. Prescribe the study medication accordingly, if the study participant require more medication.
6. Send the participant back to the appointed nurse.

Second follow-up visit (Day–7)

The process is similar to Visit–1. If the study participants and the parents miss the follow-up visit at Day-7, they can still come until the next two days (Day-8 to Day-9) after the scheduled date. The study participant will come to the nurse station, where the attending nurse will identify a patient as a study participant by the OPAL study sticker on the front page of the medical record. The nurse will measure the weight, height, body temperature, and blood pressure of the study participant. The nurse will then report this to the appointed nurse. Using the registration ID number attached on the OPAL study sticker on the front page of the medical record, the attending nurse will collect that particular subject's **case report form binder**.

The appointed nurse will:

1. Identify any adverse effects or complications since the last visit
2. Check the completeness and collect **the second mini booklet of CRF06: Symptom diary**
3. Remind the parents to complete **the third mini booklet of CRF06: Symptom diary** on the next morning until Day-14. The nurse will inform the parents that at Day-14, a research staff will visit their home to collect the diary. The research staff will also obtain feedback from the parents regarding their experience and obstacles during the past 14 days of the study, using **CRF11: Feedback form.**
4. Collect the left-over study medication from those in the prednisolone group. This will be recorded in **FORM04: Study medication return form.** The appointed nurse will complete

the study registration ID, returning date, and numbers of left-over study medication. She can add some comment regarding the use of prednisolone if necessary.

5. Report the study participant to any participating physician on duty that day, along with the **case report from binder**.
6. After the study participant finish the consultation and data collection with the participating physician, the study participant again will meet the appointed nurse. The appointed nurse will check the completeness of all study documents in the Case report form binder.
7. Record the visit date on **CRF09: Follow-up visit card**
8. Remind the parent to come for the next follow-up visit (Visit-3) at the Day 30.
9. Hand over a study souvenir (toys) and transport cost reimbursement envelope for each study participant.

The participating physician will:

1. Identify any complications of AOM and perform ENT, otoscopic, and tympanometry examination.
2. Identify the severity of AOM symptoms using VAS and AOM-SOS on **CRF05: Outcome form.**
3. Identify any side effects. If it is necessary to determine the treatment for the side effects, the physician can retrieve the information from the nurse whether the study participant was allocated to prednisolone or control group.
4. Send the study participant back to the appointed nurse.

Third follow-up visit (Day–30)

At the third visit, the patient will come on Day–30. If the study participant misses the scheduled follow-up visit, then the study participant can come on any other day up to one week after the scheduled date. Similar to previous visits, the nurse will identify the study participant using the OPAL study sticker attached on the front page of the medical record and perform a general examination. The attending nurse will report this subject to the appointed nurse. The appointed nurse will collect and prepare the **case report form binder**, and bring the study participant with the binder to the participating physician on duty.

The physician will identify whether in the past one month, the study participant experiences a new episode of ear pain or any other symptoms related to acute otitis media. The physician will also conduct a nose and throat examination, as well as an ear examination using otoscope. This information will be recorded in **CRF05: Outcome form**. The study participant will then undergo a tympanometry examination and will go back to the consultation room for the assessment of the tympanometry result. At the end of the visit, the physician will hand over the completed study documents in the **case report form binder** back to the appointed nurse where she will check the completeness of the forms and store it back in the locked filing cabinet.

Fourth follow-up visit (Day–90)

The process is similar to Visit–3. At the end of the visit, the physician will hand over the completed study documents in the **case report form binder** to the appointed nurse where the nurse will then check the completeness of the forms. The appointed nurse will collect al the study documents form the case report form binder and clip them together, and separate the document to a plastic sleeve in the **completed case report form and non-participating subject binder.** The nurse will then record

the randomisation ID, date enrolled to the study, whether the study participant come to all follow-up visits, and date of completion of the study.

Assessing Adverse Events

The appointed nurse will be the first person who identifies adverse events on the first visit at Day-3 (48 hours after the baseline visit). The adverse events will be identified by obtaining information of any unfavourable effects after taking the study medication in forms of: (1) interview and (2) the assessment of **the completed first mini-booklet of the symptom diary** (see **Appendix 1. Protocol, section 'Harms', page 25-26**).

The nurse will report any adverse events to the physician without acknowledging the study intervention that the patient has received. However, if it necessary to determine the treatment for the adverse events, the physician may have the information of intervention allocation. The physician will check other medications that have been prescribed (e.g. antibiotics, decongestants, mucolytic) at the baseline visit and obtain more detailed information regarding the adverse events to identify its correlation with trial drug or other concomitant drugs. The physician will then record this on **CRF05: Outcome form**.

The physician will record severe adverse event(S) on **CRF10: Serious adverse events reporting form** and inform this to the chief investigator (CI). The physician will report any adverse events that cause the modification or discontinuation on study medication to the CI. The decision to discontinue study medication will be determined by the physician based on the clinical judgment and the CI based on perspective of good clinical practice (GCP). If the patient requires other tests and/ treatments, the physician will provide these services. All the costs will be reimbursed by the study. However, this must be reported and recorded on **CRF05: Outcome form**.

Feedback Form

As this study is a pilot study, we will obtain information from all individuals involved in the study (i.e. participating physicians, appointed nurses, audiologists, pharmacists, study participants, and the parents) to identify their experience and obstacles that they encountered during the study.

For the participating physicians, audiologists, the appointed nurses, and pharmacists, we will obtain their feedback using **CRF11: Feedback form** in an interview session. We will interview them after they have enrolled at least five children into the study.

We will obtain the feedback from the parents at Day-14 during the home visit. The home visit will be conducted to collect the **third mini-booklet of the symptom diary**, where we will also interview the parents to obtain the feedback using **CRF11: Feedback form**.

Closing Out The Study

When closing out the study, the research team will check several documents to validate the compatibility and the completeness of the data:

1. **FORM01: Study recruitment log book**, will be checked for its compatibility with **CRF01: Consent form; CRF03: Eligibility form;** and **CRF08: Randomisation form** in the **case report form binder** of each study participant.
2. The completeness and the date of follow-up visit in **CRF05: Outcome form**, will be checked for its compatibility with the visit dates on **CRF06: Symptom diary** and **CRF09: Follow-up visit card**.
3. The number of **CRF11: Feedback form will** be checked for its compatibility with the number of participating physicians, audiologists, appointed nurses, pharmacies, and the parents who are involved in the study

In regards to study medication, the research team will check the numbers of unused medication at the pharmacy and the left-over medicine on the parents, and compare the numbers with **FORM03: Study medication dispensing form; FORM04: Study medication return form;** and the number of used paper-packs accordingly.

In regards to administrative work, the research team will:

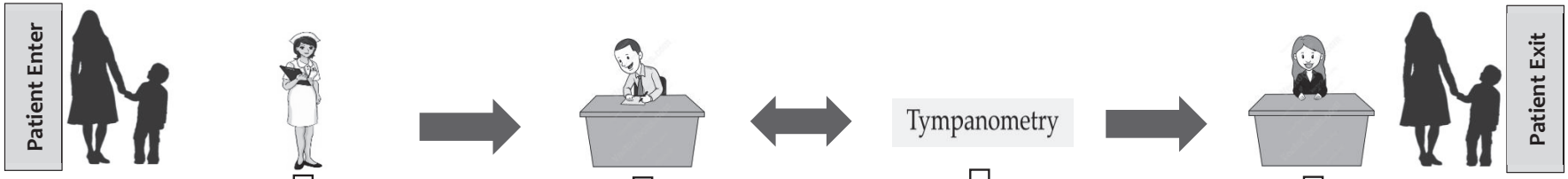
1. Collect the left-over envelopes for the reimbursement of patients' transportation cost and check the compatibility with the numbers of follow-up visits recorded in **CRF09: Follow-up visit card.**
2. Confirm the hospital cashier regarding the study-related payment (e.g. registration fee, tympanometry examination, any additional test or treatment due to adverse events) according approved Memorandum of Agreement (MoU) with the numbers of follow-up visits recorded in **CRF09: Follow-up visit card** and **CRF05: Outcome form** for any additional tests or treatments for side effects.
3. Confirm the inventory list with the starting kit container.

At the end of study, as part of the dissemination of the study results, the research team will:

1. Provide a study summary that will include the examination results of individual study participants and the overall result of the study to each participant.
2. Provide a report document of the study to the Bond University's Human Research Ethics Committee, the Research Committee Ethics Faculty of Medicine Universitas Indonesia (FMUI) – Dr. Cipto Mangunkusumo Hospital (CMH), and all participating hospitals.

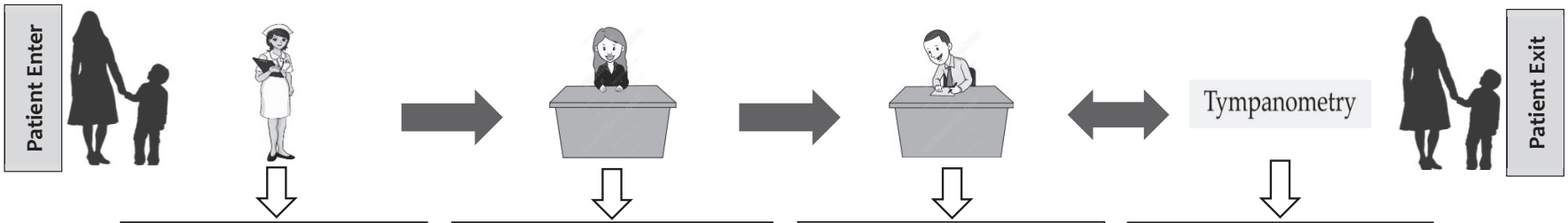
Appendix 1. Patient flow chart

Baseline Visit (Visit-0)



Attending Nurse	Physician	Audiologist	Appointed nurse
• Identifying potential AOM patients using the checklist on the study registration log book • Preparing the case report form (CRFs) • Collecting data of body weight, height, body temperature, and blood pressure • Preparing and handing over the study document (I.e. study recruitment log book, CRFs) to the physician	• Eligibility assessment • Stratification process • Baseline history taking • Outcomes assessment using CRF and otoscope • Providing a symptom diary and training • Providing study medication prescriptions • Checking and interpreting the tympanometry findings	• Outcomes assessment using tympanometry	• Randomisation • Study medication prescription dispensing • Study document collection and storage • List the follow-up visits on the follow-up reminder card • Hand over the study bag • Reimbursing the transport costs

Other visits (Visit-1 to Visit-4)



Attending Nurse	Appointed Nurse	Physician	Audiologist
• Collecting data of body weight, height, body temperature, and blood pressure • Preparing and handing over the case report form (CRFs) to the appointed nurse	• Checking the completion of study document • Identification adverse effects and complications • Checking the symptom diary • Checking the number of study medication, whether they will be available for the next two days • Completing the follow-up reminder card • Collecting the first mini-booklet of symptom diary and provide the second mini booklet at Visit-1 • Handing over the study document and reporting any adverse effects or complications to the physician • Collecting the second mini-booklet of symptom diary and provide the third mini booklet at Visit-2 • Collecting the left-over drug (prednisolone group) at Visit–2 and completing the drug dispensing and returning form	• Identification adverse effects and complications • Outcomes assessment using CRF and otoscope • Checking the symptom diary • Checking and interpreting the tympanometry findings • Checking the additional medication	• Outcomes assessment using tympanometry

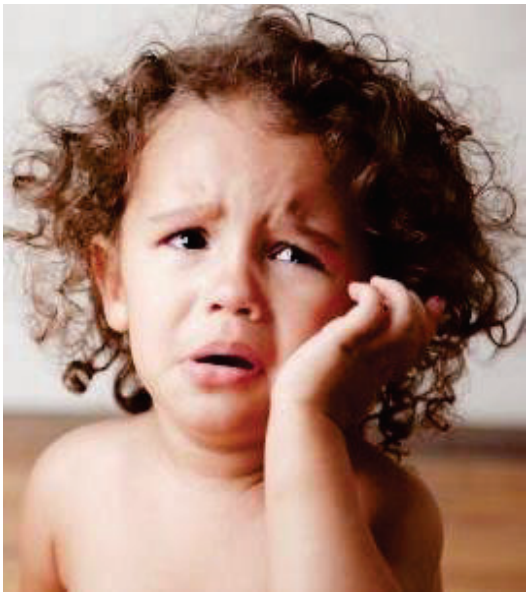
Appendix 4.4. Training slides

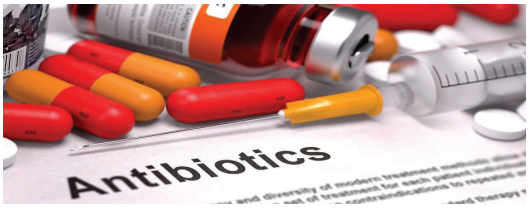
Oral Prednisolone for Acute otitis media in chiLdren: a pilot pragmatic, randomised, open-label, single-blind study (OPAL Study)

Clinical Epidemiology and Evidence-Based Medicine Unit
Dr Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia

Centre for Research in Evidence-Based Practice
Faculty of Health Sciences and Medicine Bond University

STUDY SUMMARY 1





Background (1)

2

Background (2)

3

60% of AOM cases will be resolved in 24 hours

Treatment

Pain management

Observation

Antibiotics

80% of AOM cases will be resolved in 72 hours

Australia: 89% of new AOM cases were treated with antibiotics (2010 – 2015).
Our survey study (2016) demonstrated that 88% of physicians would prescribe antibiotics for mild AOM.

Alternative treatment for AOM

Corticosteroids

Clinical practice guidelines
versus
Daily clinical practice

Clinical trials of corticosteroids for AOM

Cochrane Library

Cochrane Database of Systematic Reviews

Systemic corticosteroids for acute otitis media in children (Protocol)

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB

Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, Del Mar CB.
Systemic corticosteroids for acute otitis media in children.
Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD012289.
DOI: 10.1002/14651858.CD012289.

www.cochranelibrary.com

Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes

Aino Ruohola, MD, Terho Heikkinen, MD, Jussi Jero, MD, Tuomo Puhakka, MD, Taina Juvén, MD, Mervi Närkiö-Mäkelä, MD, Harri Saxén, MD, and Olli Ruuskanen, MD

Objective: To determine the efficacy of a short course of oral prednisolone as an adjuvant therapy for acute otitis media draining through tympanostomy tubes.

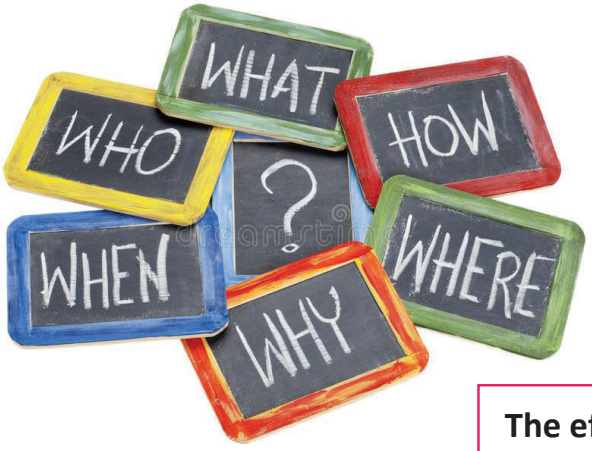
Study design: In a randomized, double-blind, placebo-controlled study, children with acute discharge (<48 hours) through tympanostomy tubes received either prednisolone (2 mg/kg/d; n = 23) or placebo (n = 27) for 3 days. All children received amoxicillin/clavulanate (40/10 mg/kg/d) for 7 days. The children were examined daily at the study clinic until the drainage ceased.

Results: The median duration of otorrhea in the prednisolone group was 1.0 days (25% to 75% range, 1.0 to 2.0 days), compared with 3.0 days (25% to 75% range, 2.0 to 4.0 days) in the children receiving placebo ($P < .001$). The duration of otorrhea was ≤2 days in 21 (91%) children in the prednisolone group, compared with 8 (30%) children in the placebo group ($P < .001$).

Conclusions: Oral prednisolone appears to be modestly effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes in children. Further studies seem warranted to determine whether short-term use of steroids early during the course of acute otitis media would also reduce the duration of middle ear effusion in children with intact tympanic membranes. (J Pediatr 1999;134:459-63)

Research question

6



Research Gap

↓

A quality clinical trial

↓

The effectiveness of corticosteroids as a monotherapy or as an addition to antibiotics for AOM

A pragmatic, parallel, randomized, placebo-controlled, double blind study of corticosteroids for AOM in children

Prednisolone

7

PREDNISOLONE

Doses	Frequency	Duration
10 mg/day: aged 6 months to < 2 years 20 mg/day: aged 2 years to < 6 years 30 mg/day: →aged 6 years to 12 years	Once a day, in the morning	5 (five) days
Otitis media clinical trial and national/international guidelines of paediatric infectious and inflammation disorders.	Single dose to prevent the suppression of hypothalamic-pituitary-adrenal (HPA) axis	Ranged 3 to 7 days
Range of prednisolone dose: 0.25 – 2 mg/kg body weight/day		AOM cytokines peaked: 3 hours to 3 days. Progressively decreased: 4 to 6 days Normalization: > 6 days

Side effects?

Objectives of the study

Primary objectives	To assess the overall process and procedures of a large main study, including (1) the recruitment criteria; (2) the process of stratification and randomisation; (3) clinical outcomes measures using validated and customized tools.
	To identify any practical and operational issues that potentially occur in the large main study.
	To verify a sample size calculation for the large main study.
Secondary objectives	To identify and explain the mechanism of corticosteroids in improving middle ear effusion and other clinical symptoms of AOM in a mechanistic sub-study using tympanometry.

A Pilot study and a mechanistic sub-study

P	Children aged 6 month to 12 years with acute otitis media (AOM) [N=60].
I	Oral prednisolone plus expectant observation (mild AOM) OR Oral prednisolone plus antibiotics (severe AOM)
C	Without prednisolone plus expectant observation (mild AOM) OR Without prednisolone plus antibiotics (severe AOM)
O	Recruitment rates The success of study procedures Ability to measure planned outcomes in main study Compliance to study and study drug The verification of sample size calculation for main study
	The change in middle ear effusion at various time points Duration of middle ear effusion The correlation between ear pain and other symptoms with the changes in MEE at various time points
T	9 months [Dr Cipto Mangunkusumo Hospital, Persahabatan Hospital, Gatot Soebroto Army Hospital, Antam Medika Hospital, Islamic Hospital, Proklamasi ENT Hospital]

Study timeline

10

	STUDY PERIOD				
	Enrolment Allocation	Post-allocation			Close-out
TIMEPOINT	0	t_1 (day-3 to -5)	t_2* (day-7 to -9)	t_3* (day-30 to -40)	t_4* (day-90 to -100)
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation	X				
INTERVENTIONS:					
[Intervention A] Prednisolone		—	—		
[Intervention B] Control		—	—		
ASSESSMENTS:					
Baseline examination (weight, height, BP, temperature)	X	X	X	X*	X*
Severity of pain and duration using VAS	X	X	X		
Overall symptoms and its duration using AOM-SOS	X	X	X		
Adherence to trial drug	X	X	X		
Adverse effects	X	X	X		
Otoscopic examination	X	X	X	X**	X**
Tympanometry examination	X+	X+	X+	X+	X+
Complication	X	X	X		
Recurrence of AOM				X*	X*

Recruitment process

11

CRF01. Information sheet and consent form

The research summary
The overall procedures in the study, including the follow-up visit
Potential side effects
Compensation
Voluntary participation

CRF03. Eligibility form

Mild AOM	Severe AOM
• Mild ear pain • fever < 39°C • Otoscopy: mild bulging • Complication (-)	• Moderate to severe ear pain • Fever ≥ 39°C • Otoscopy: moderate-to-severe bulging, suppurative appearance • Children aged < 2 years with bilateral AOM • AOM with tympanic membrane perforation

Initial screening [Attending nurse & Phycisian] → **Consent to study** [Physician] → **Recruitment based on eligibility criteria** [Physician] → **Stratification** [Physician]

FORM01. Study recruitment log book

Ear pain in the past 48 hours
OR
Holding/pulling out the ear, irritable in the past 48 hours
OR
Experiencing ear discharge in the past 48 hours

CRF03. Eligibility form

Inclusion criteria	Exclusion criteria
children (6 months – 12 years) with AOM, defined as a current onset within 48 hours of ear-related symptoms (e.g. ear pain, ear tugging/rubbing or irritability) and if possible to assess, otoscopic findings of acute inflammation (e.g. erythema) and middle ear effusion (e.g. bulging, air-fluid level)	Children with or who: 1. major and severe medical conditions (e.g. heart/kidney failure) 2. immunocompromised children (e.g. HIV, in cancer treatment) 3. congenital malformations and/or syndromes (e.g. cleft palate) 4. high risk of strongyloidiasis infection 5. ear ventilation tube(s) 6. had exposed to persons with varicella or active Zoster infection in the past 3 weeks without any prior varicella immunization/ infection 7. have taken oral or topical steroids in the preceding four weeks 8. have taken antibiotics in the preceding two weeks 9. are hypersensitive to prednisolone other corticosteroids.

Data collection

12

Outcome identification [Physician] → **Tympanometry examination [Audiologist & Physician]** → **Randomisation [An appointed nurse for randomosation]**

CRF04. Baseline information form
CRF05. Outcome form
CRF06. Symptom diary
CRF07. Prescription of study medication
FORM07. Guideline of antibiotics for AOM
FORM08. Prednisolone dose for OPAL study

Baseline information and history
General examination
ENT examination, including otoscopy
Tympanometry examination
Severity of AOM symptoms using VAS and AOM-SOS
Complications of AOM
Previous and current treatment
Prescribe the study medication (and antibiotics for severe AOM) and other symptomatic medications
Teach how to complete a symptom diary

CRF05. Outcome form

Tympanometry examination
Interpret the tympanometry results

CRF08. Randomisation form

Mild AOM		Severe AOM	
Observation + Prednisolone	Observation alone	Antibiotics + Prednisolone	Antibiotics alone

Case report form binder
Confidential study document binder

Check the completeness all study documents and separate the confidential ones to the confidential study document binder, as follows:
Confidential study document binder: (1) FORM01. Study recruitment log book; (2) CRF01. Consent form; (3) CRF02. Study registration form; and (4) CRF08. Randomisation form.
Case report form: (1) CRF03. Eligibility form; (2) CRF04. Baseline information form; (3) CRF05. Outcome form; (4) CRF10. Serious adverse event reporting form; (5) CRF11. Feedback form

CRF07. Prescription of study medication
CRF06. Symptom diary
CRF09. Follow-up visit card
FORM09. Instruction of prednisolone use for parents
FORM10. Lupred pharmaceutical brochure
CRF02. Study registration form

Dispense the prescription of study medication (prednisolone group), including provide the Information of prednisolone use
Confirm the completion of symptom diary
Complete the study registration form
Observation and identification of complication and side effects
Follow-up visits and the card
Keep the intervention allocation confidential
Provide study souvenirs and transport reimbursement

13

INITIAL SCREENING (by attending nurse)

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine (CEEBM) Unit Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, single-blind study (OPAL Study)

FORM01 – STUDY RECRUITMENT LOG BOOK

Nurse name/ID : | **Study title :** Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, single-blind, controlled study (OPAL study) | **Hospital ID :**

Study registration ID	Patient's name	Date screened	Has your child experien-cing ear pain in the past 48 hours? (YES or NO)	Has your child been tugging or rubbing her/his ear(s) and been more irritable or fussy or crying more than usual over the past 48 hours (YES or NO)	Has your child been experie ncing ear discharg e in the past 48 hours? (YES or NO)	Body weight (kg)	Body height (cm)	Body tempe-rature (°C)	Blood pressure (mmHg)	Did patient go on the study? (YES or NO)	If YES, what is the Randomisation ID	If NO, please tell us reason not on the study below		
												Not eligible (YES or NO)	Did not give consent (YES or NO)	Was not approached (YES or NO). Write the reason

14

CONSENT TO THE STUDY (1)

REGISTRATION ID

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind study (OPAL Study)

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Oral prednisolone for acute otitis media in children: a pilot pragmatic randomised open-label single-blind controlled study (OPAL study)
[Steroids for middle ear infection in children]

Invitation
You are invited to participate in a research study into the use of steroids (prednisolone) or an anti-inflammatory drug for middle ear infection in children.

The study is being conducted by Dr. Respati W. Ranakusuma, an otorhinolaryngologists and a researcher at the Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit Dr. Cipto Mangunkusumo Hospital–Faculty of Medicine Universitas Indonesia. This is part of an international collaborative study between CEEBM CMH-FMUI and the Centre for Research in Evidence-Based Practice (CREBP), Faculty of Health Sciences and Medicine Bond University, Queensland, Australia.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is the purpose of this study?
   The purpose is to investigate whether steroids, as an alternative treatment, will reduce ear pain and other symptoms in children with acute or recent (less than 48 hours) middle ear infection. This study is part of a doctoral project at the CREBP Bond University, Queensland, Australia. As this is a pilot study, we also want to know your experience during the study. For example, the obstacles you found in giving the steroid to your child or completing the symptom diary daily.

2. Why have my child and I been invited to participate in this study?
   Your child and you have been invited to participate in this study because your child age ranges between six months to 12 years and having symptoms and signs of acute middle ear infection, such as ear pain in the past 48 hours, or holding or tugging her/his ear more frequently, more irritable, show lack of playfulness and/sleep in a young age (baby). If visible, from the ear examination using an otoscope, the ear drum(s) will show redness or yellowish, bulging, or discharge. Otoscope is a tool consisted of a lamp, magnifying glass, and a silicone/plastic probe that will be inserted into the ear canal to identify the condition of the ear canal and ear drum. This examination is painless.

3. What does participation in this study involve?
   If you agree to participate in this study, your physician will ask you more questions regarding the history of your

CONSENT FORM

Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind study (OPAL study)
[Steroids for middle ear infection in children]

1. I, _____
   of _____
   agree to participate in the study described in the participant information statement set attached to this form.
2. I acknowledge that I have read the participant information statement, which explains why my child has been selected, the aims of the study, and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.
3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm my child might suffer as a result of my child participation and I have received satisfactory answers.
4. I understand that I can withdraw from the study at any time without prejudice to my relationship to my physician and the _____ Hospital.
5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.
6. I understand that I have any questions relating to my participation in this research, I may contact Dr. Respati W. Ranakusuma, ORL on telephone +62 8111 012 185, who will be happy to answer them.
7. I acknowledge receipt of a copy of this Consent Form and the Participation Information Statement.

Complaints may be directed to the OPAL Study Support Office at the Clinical Epidemiology and Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia, Building H Dr Cipto Mangunkusumo Hospital, Diponegoro 71, Jakarta 10430, Indonesia (phone +62 21 316 1760, email OPAL.study@bond.edu.au).

Signature of participant aged 12 years old	Name	Date
_____	_____	_____
Signature of the parent	**Name**	**Date**
_____	_____	_____
Signature of witness	**Name**	**Date**
_____	_____	_____

15

CONSENT TO THE STUDY (2)

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. I will collect all clinical information throughout clinical history taking, general examination, and ear, nose, and throat assessment (using otoscope, tympanometry in some cases), questionnaires/forms, feedback forms, and symptom diary
2. The patient has to come to the hospital for four times following the first visit for three months
3. The patient will be located to treatment with antibiotic or 48-hours observation with re-assessment at the end of the observation. Either way, the patient will receive a research medicine (prednisolone) or without
4. The patient or patient's parent(s) or the parents are aware of any potential unwanted effects that may occur during the research
5. The patient or patient's parent(s) should record the patient's condition, the adherence of trial drug intake, and unwanted effects by completing a symptom diary that will provided at the first visit

I confirm that the participant (patient and/or patient's parent(s)) was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Signature of investigator	Name	Date
_____	_____	_____

REVOCATION OF CONSENT

Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind study (OPAL study)
[Steroids for middle ear infection in children]

I hereby wish to WITHDRAW my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with the _____ hospital or my medical attendants.

Signature of participant or the parent	Name	Date
_____	_____	_____

The section for Revocation of Consent should be forwarded to Dr. Respati W. Ranakusuma, ORL at the Clinical Epidemiology and Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia.

Obtaining the consent to the study

16

In obtaining and documenting IC, the investigator should comply with the applicable regulatory requirement(s), GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

The subject or the subject's legally acceptable representative should be informed in a timely manner if new relevant information becomes available. The communication of this information should be documented.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

None of the oral and written information concerning the trial, including the written IC form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator / institution for negligence.

The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide IC, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

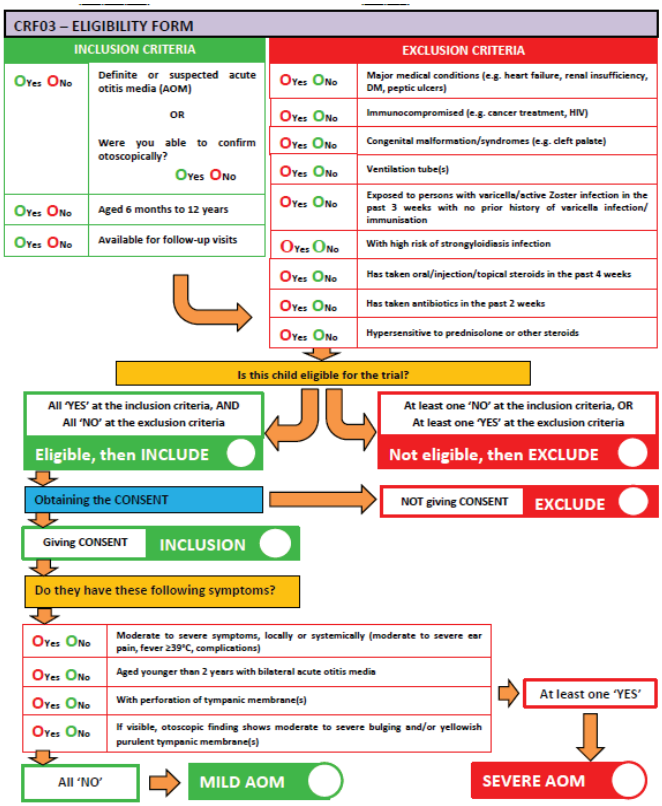
Information in the consent form

17

The trial involves research	Purpose of the trial	The trial treatment(s) & the probability for random assignment to each treatment.	The trial procedures to be followed	The subject's responsibilities.
Those aspects of the trial that are experimental	The reasonably foreseeable risks or inconveniences to the subject	The reasonably expected or no intended benefits, including the risks	The alternative procedure(s) or course(s) of treatment that may be available to the subject, including important potential benefits and risks.	The compensation and/or treatment available to the subject in the event of trial related injury.
The anticipated prorated payment and anticipated expenses (if any)	Voluntary participation and the subject may refuse to participate or withdraw from the trial, at any time	The auditor(s) or IRB/IEC will be granted direct access to the subject's medical records for verification of clinical trial procedures	The records identifying the subject will be kept confidential	the subject or the subject's legally representative will be informed if relevant information becomes available
	The person(s) to contact for further information regarding the trial , including trial-related injury events	The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.	The expected duration of the trial, including the approximate number of subjects involved in the trial.	

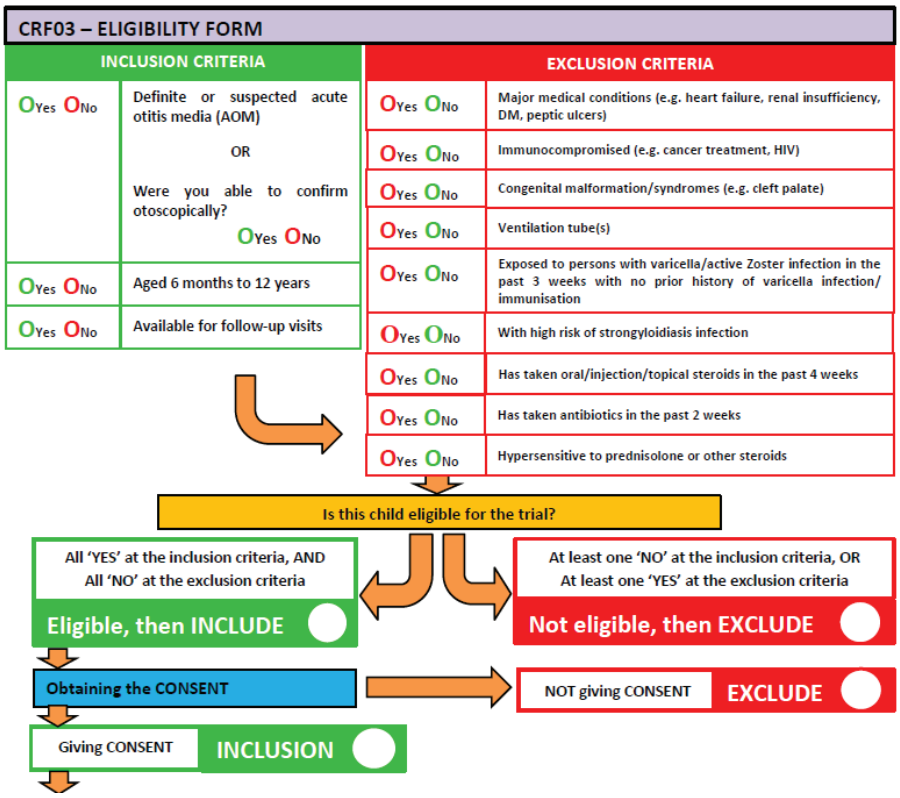
18

ELIGIBILITY CRITERIA (by Physician)



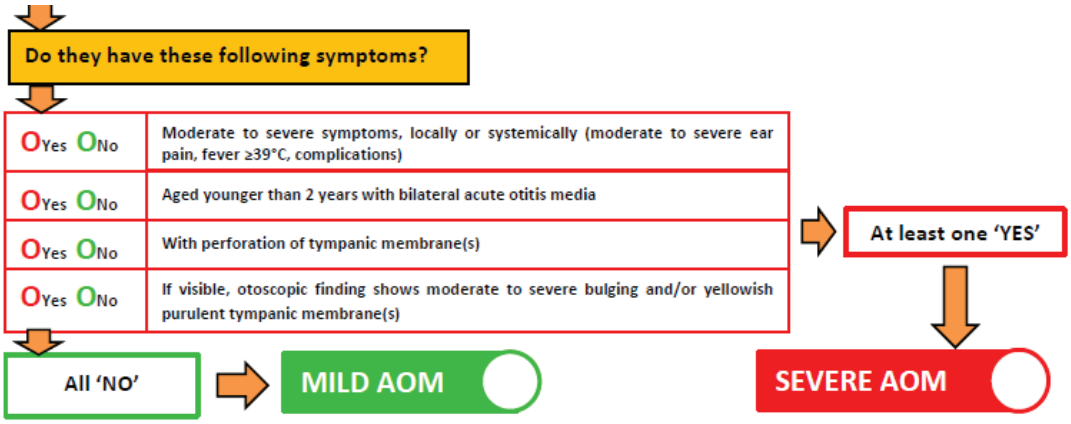
19

ELIGIBILITY CRITERIA (by Physician)



20

ELIGIBILITY CRITERIA (by Physician)



21

ELIGIBILITY RESULT (by Physician)

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine (CEEBM) Unit Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, single-blind study (OPAL Study)

FORM01 – STUDY RECRUITMENT LOG BOOK

Nurse name/ID :	Study title : Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, single-blind, controlled study (OPAL study)	Hospital ID :

Study registration ID	Patient's name	Date screened	Has your child experien-cing ear pain in the past 48 hours? (YES or NO)	Has your child been tugging or rubbing her/his ear(s) and been more irritable or fussy or crying more than usual over the past 48 hours (YES or NO)	Has your child been experie ncing ear discharg e in the past 48 hours? (YES or NO)	Body weight (kg)	Body height (cm)	Body tempe-rature (°C)	Blood pressure (mmHg)	Did patient go on the study? (YES or NO)	If YES, what is the Randomisation ID	If NO, please tell us reason not on the study below		
												Not eligible (YES or NO)	Did not give consent (YES or NO)	Was not approached (YES or NO). Write the reason

CRF04 – BASELINE INFORMATION FORM

1 Did (do) you breastfeed your child? O Yes O No

If ' YES', until the age of O ≤ 2 months O > 2 – 6 months O > 6 months

2 Does your child attend a day-care O Yes O No

How many days in a week? O ≤ 2 days O > 2 days

3 Have your child had a pneumococcus vaccine (PCV)? O Yes O No O Do not know

How many times: _____ times

4 Have your child had an influenzae vaccine? O Yes O No O Do not know

How many times: _____ times

5 How many episodes of recurrent acute respiratory infection (runny nose, cough, sore throat, fever) in the past year? O ≤ 3 episodes O > 3 episodes to 6 episodes O > 6 episodes

6 Did your child have a history of 3 or more episodes of ear infection (ear pain, ear discharge, diarrhoea, or vomiting) during the past 12 months? O Yes O No

7 At what age did the first episode of ear infection start?

O ≤ 6 months O > 6 to 12 months O >12 to 24 months O > 2 to 5 years O > 5 years

8 Does your child have one of the following disorders:

O Bronchial asthma

O Allergic rhinitis

O Family history of atopic disorders

O None of above

9 Number of children (including the patient) who live in the house _____ children

10 Number of persons who smoke at home _____ person(s)

CRF05 – OUTCOME FORM

Baseline Visit (Day-0) : |__|__| – |__|__| – 20 |__|__|

Complications (for Physician)

1 Does your child experience discharge from the ear(s)? O Yes O No

2 Does your child experience intense ear pain and pain behind the ear? O Yes O No

3 Does your child experience swelling/bulging/ or redness/tenderness of the ear(s)? O Yes O No

4 Does your child experience facial asymmetry (e.g. when the child smiles, cries)? O Yes O No

General and ENT examination (for Nurse and Physician)

5-1 Weight _____ kg | 5-2 Height _____ cm | 5-3 Temp. _____ °C | 5-4 BP ____/____ mmHg

6 Nose O Normal O Oedema O Hyperaemic O Livid O Serous discharge O Mucoid discharge

7 Tonsils O Normal O Hyperaemic O Detritus O Tonsil(s) T1 O Tonsil(s) T2 O Tonsil(s) T3-4

8 Pharynx O Normal O Hyperaemic O Oedema O Granules O Post nasal drip (PND)

9 Otoscopic examination

O Normal O Cerumen O Erythema O Air fluid level O Complete effusion O Opacification

O Mild bulging O Moderate to severe bulging (bulging rounded) O Bulla O Perforation

10 Medicines that have been taken before the baseline visit (please circle your dose measurement)

1. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
2. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
3. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
4. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
5. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day

Medicines prescribed by physician (you) at the baseline visit

Antibiotic _____ Dose : _____mg / BW kg Frequency : _____ / day for _____ days

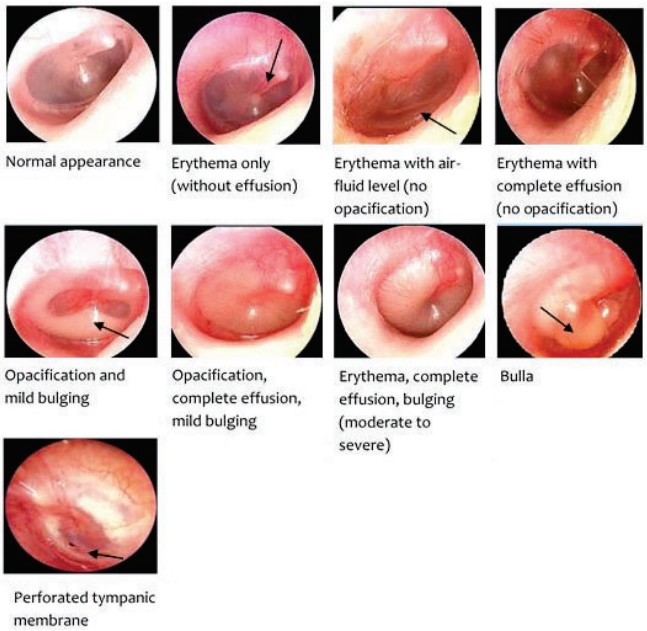
Other medicine(s)

1. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
2. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
3. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
4. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day
5. _____ Dose : _____mg perBw kg / Teaspoon / Tablespoon ; Frequency : ____ / day

Outcome: Symptoms (for patients and the parents. Physician will help them to complete these in the symptom diary)

11 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours?

No Pain — Pain As Bad As It Could Possibly Be

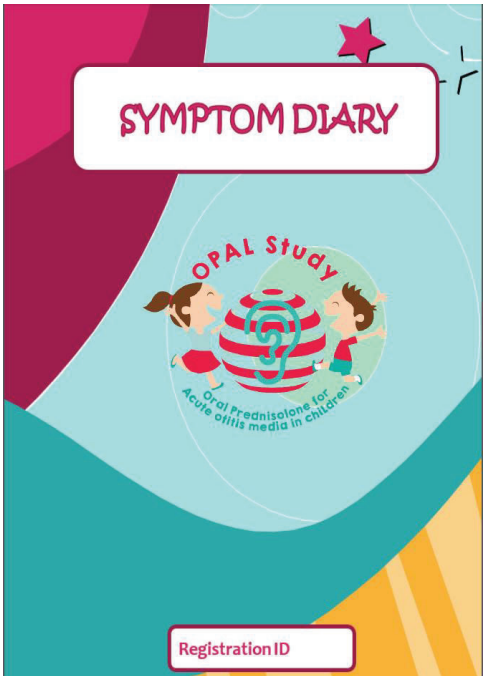


Normal appearance | Erythema only (without effusion) | Erythema with air-fluid level (no opacification) | Erythema with complete effusion (no opacification)

Opacification and mild bulging | Opacification, complete effusion, mild bulging | Erythema, complete effusion, bulging (moderate to severe) | Bulla

Perforated tympanic membrane

2 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours? (if applicable)	
No Pain — Pain As Bad As It Could Possibly Be	
3. We are interest finding out how your child has been doing. For each question, please place a checkmark (V) in the circle corresponding to your child's symptoms. Please answer all questions (if applicable).	
3.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No O A little O A lot
3.2 Over the past 12 h, has your child been crying more than usual?	O No O A little O A lot
3.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No O A little O A lot
3.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No O A little O A lot
3.5 Over the past 12 h, has your child been less playful or active than usual?	O No O A little O A lot
3.6 Over the past 12 h, has your child been eating less than usual?	O No O A little O A lot
3.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No O A little O A lot



dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pilot pragmati, randomised, open-label, single-blind, controlled study (OPAL Study)

FORM07. GUIDELINE OF ANTIBIOTICS FOR ACUTE OTITIS MEDIA

Initial immediate or delayed antibiotic therapy		Antibiotics after 48-72 hours of failure of initial antibiotic therapy	
Recommended first-line treatment	Alternative treatment (if penicillin allergy)	Recommended first-line treatment	Alternative treatment
Amoxicillin (80-90 mg/kg per day in 2 divided doses) OR Amoxicillin-clavulanate[a] (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day clavulanate (amoxicillin to clavulanate ration, 14:1) in 2 divided doses)	Cefdinir (14 mg/kg per day in 1 or 2 doses) Cefuroxime (30 mg/kg per day in 2 divided doses) Cefpodoxime (10 mg/kg per day in 2 divided doses) Ceftriaxone (50 mg IM or IV per day for 1 or 3 days)	Amoxicillin-clavulanate[a] (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day in 2 divided doses) OR Ceftriaxone (50 mg IM or IV per day for 3 days)	Ceftriaxone, 3 days Clindamycin (30-40 mg/kg per day in 3 divided doses), with or without third-generation cephalosporin (50 mg IM or IV per day for 3 days) Failure of second antibiotic Clindamycin (30-40 mg/kg per day in 3 divided doses) plus third-generation cephalosporin Tympanocentesis[b] Consult specialist[b]

[a] *may be considered in patients who have received amoxicillin in the previous 30 days or who have the otitis conjunctivitis syndrome;*
[b] *Perform tympanocentesis/drainage if skilled in the procedure, or seek a consultation from an otolaryngologist for tympanocentesis/drainage if the tympanocentesis reveals multidrug/resistant bacteria, seek an infection disease specialist consultation.*

Reference: Lieberthal AS, Carroll AE, Chonmaitree T, et al. Clinical Practice Guideline: The diagnosis and management of acute otitis media. The American Academy of Pediatrics. *Pediatrics.* 2013;131:e964-e99

26

GUIDELINE OF PRDNISOLONE DOSE FOR OPAL STUDY

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind, controlled study (OPAL Study)

FORM08 – PREDNISOLONE DOSE FOR OPAL STUDY

Aged six months to up to two years old	Dose : 10 mg / day (2 tablets per day)	10 tablets of Prednisolone for five days
Aged two years to up to six years old	Dose : 20 mg / day (4 tablets per day)	20 tablets of Prednisolone for five days
Aged six years to 12 years old	Dose : 30 mg / day (6 tablets per day)	30 tablets of Prednisolone for five days

Lupred® 5 contains 5 mg prednisolone in each tablet

27

PRESCRIPTION OF STUDY MEDICATION (by Physician)

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind, controlled study (OPAL Study)

Date _____

CRF07. Prescription for OPAL study medication

Prednisolone doses:

- Aged 6 months to < 2 years old = 10 mg per day
- Aged 2 years to < 6 years old = 20 mg per day
- Aged 6 years to 12 years old = 30 mg per day

Registration ID : ☐

Name : _____

Age : _____ months / year(s) *[write and circle your answer]*

Study medication dose : _____ mg per day = _____ tablets per day

R/ OPAL study medication tablet .....

Sach lact add

m.f. pulveres dtd No. V

∫ 1 dd 1 pc (before 9 am)

_____

(sign here)

28

RANDOMISATION (by Appointed Nurse)

REGISTRATION ID | | | | |

Nurse ID : |___|___|___| Site ID : |___|___|___| Date : |___|___| – |___|___| – 201 |___|

CR08 – RANDOMISATION FORM

Eligibility criteria (cross-check with 'FORM01. study registration log book', and 'CRF03. Eligibility form' in the 'Case Report Form Binder' of this subject).

All YES for all inclusion criteria	O Yes	O No
All NO for all exclusion criteria	O Yes	O No

Consent to the study questions (cross-check with 'CRF01. Informed consent' in the 'Case Report Form Binder' of this subject).

Has consent given?	O Yes	O No

RANDOMISATION

Father's mobile phone number									
Mother's mobile phone number									
Severity of AOM	**O Mild AOM**						**O Severe AOM**		
Subject's date of birth	Date		Month		Year		**AGE**		Month/year

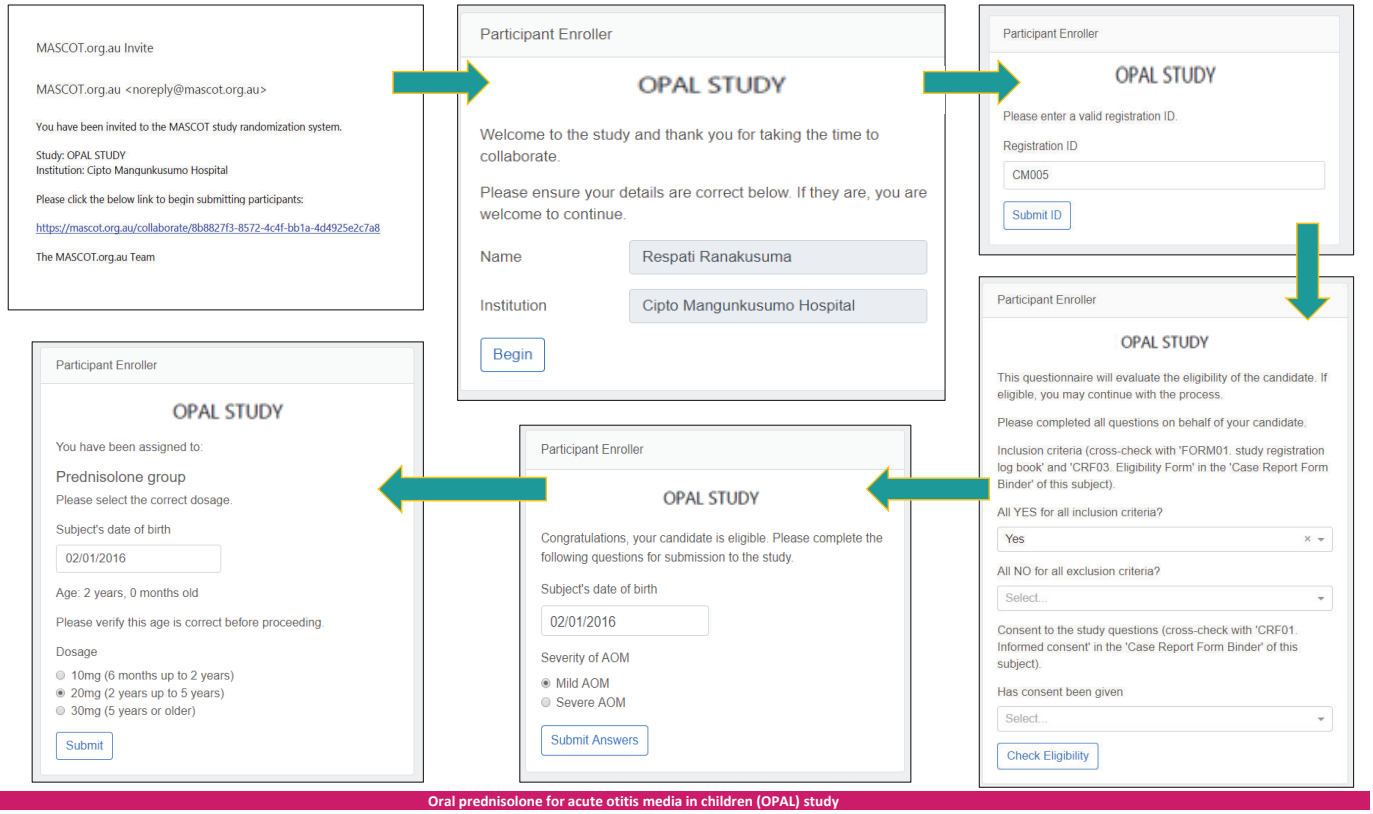
RANDOMISATION RESULT

Randomisation ID			
This subject is allocated to	**O Prednisolone group**		**O Control group (no prednisolone)**
Prednisolone dosage (if the subject is allocated to prednisolone group)	**O 10 mg/day**	**O 20 mg/day**	**O 30 mg/day**

Nurse's signature		Nurse's name		Date	

29

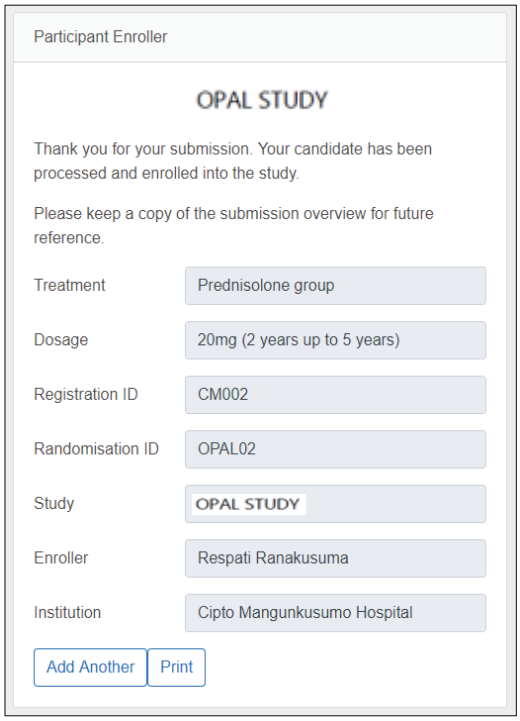
RANDOMISATION BY RANDOMISATION SYSTEM WEBSITE



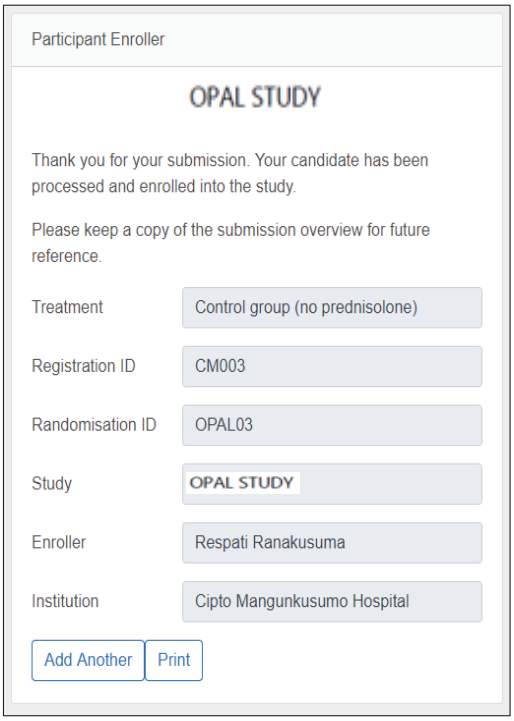
30

RANDOMISATION BY RANDOMISATION SYSTEM WEBSITE

PREDNISOLONE GROUP



CONTROL GROUP



31

RANDOMISATION BY PHONE

RANDOMISATION STARTS → CALL RANDOMISATION CALL-CENTRE → PROVIDE RANDOMISATION INFORMATION

Registration ID label	Registration ID
CRF03. Eligibility form	All 'YES' for all inclusion criteria
CRF03. Eligibility form	All 'NO' for all inclusion criteria
CRF01. Consent form CRF03. Eligibility form	Has consent been given?
CRF08. Randomisation form	Date of birth and age of the patient
CRF07. Prescription FORM08. Prednisolone dose for OPAL study	Dose of the prednisolone
CRF03. Eligibility form	Severity of AOM

RANDOMISATION CALL-CENTRE WILL ACCESS THE RANDOMISATION SYSTEM → RANDOMISATION CALL-CENTRE PROVIDE RANDOMISATION RESULTS

- Randomisation ID
- Treatment group
- Prednisolone dose for those allocated in the prednisolone group

RECORD THE RANDOMISATION RESULT TO CRF08. RANDOMISATION FORM

32

CLOSING THE INIATIAL VISIT (by Appointed Nurse)

Dispensing CRF07.Prescription of study medication for children allocated to Prednisolone group

Provide FORM09. Instruction of prednisolone use for parents whose children were allocated to the Prednisolone group

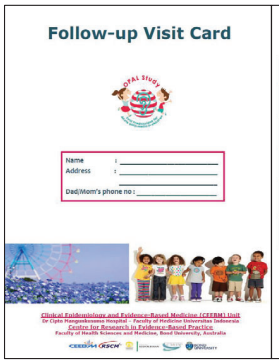
Reimbursement for transportation cost

Study souvenirs

Follow-up visit card

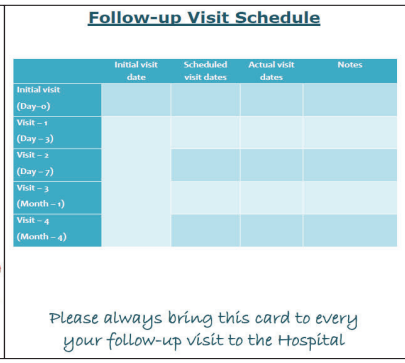
Confirming the ability of parents to complete CRF05. Symptom diary

Completion of CRF02. Study registration form by the parents


Follow-up Visit Card

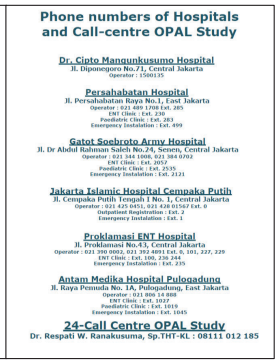
Name :
Address :
Dad/Mom's phone no :

Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit
Dr Cipto Mangunkusumo Hospital - Faculty of Medicine Universitas Indonesia
Centre for Research in Evidence-Based Practice
Faculty of Health Sciences, Bond University, Australia


Follow-up Visit Schedule

	Initial visit date	Scheduled visit dates	Actual visit dates	Notes
Initial visit (Day–0)				
Visit – 1 (Day – 3)				
Visit – 2 (Day – 7)				
Visit – 3 (Month – 1)				
Visit – 4 (Month – 4)				

Please always bring this card to every your follow-up visit to the Hospital


Phone numbers of Hospitals and Call-centre OPAL Study

Dr. Cipto Mangunkusumo Hospital
Jl. Diponegoro No.71, Central Jakarta
Operator : 1500135

Persahabatan Hospital
Jl. Persahabatan Raya No.1, East Jakarta
Operator : 021 489 1708 Ext. 205
ENT Clinic : Ext. 230
Paediatric Clinic : Ext. 283
Emergency Instalation : Ext. 499

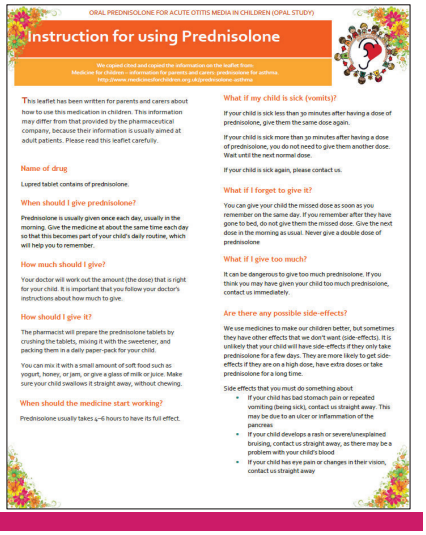
Gatot Soebroto Army Hospital
Jl. Dr Abdul Rahman Saleh No.24, Senen, Central Jakarta
Operator : 021 344 1008, 021 384 0702
ENT Clinic : Ext. 2057
Paediatric Clinic : Ext. 2535
Emergency Instalation : Ext. 2121

Jakarta Islamic Hospital Cempaka Putih
Jl. Cempaka Putih Tengah I No. 1, Central Jakarta
Operator : 021 425 0451, 021 428 01567 Ext. 0
Outpatient Registration : Ext. 2
Emergency Instalation : Ext. 1

Proklamasi ENT Hospital
Jl. Proklamasi No.43, Central Jakarta
Operator : 021 390 0002, 021 392 4091 Ext. 0, 101, 222, 229
ENT Clinic : Ext. 100, 230 244
Emergency Instalation : Ext. 235

Antam Medika Hospital Pulogadung
Jl. Raya Pemuda No. 1A, Pulogadung, East Jakarta
Operator : 021 806 14 888
ENT Clinic : Ext. 1017
Paediatric Clinic : Ext. 1019
Emergency Instalation : Ext. 1045

24-Call Centre OPAL Study
Dr. Respati W. Ranakusuma, Sp.THT-KL : 08111 012 185


ORAL PREDNISOLONE FOR ACUTE OTITIS MEDIA IN CHILDREN (OPAL STUDY)

Instruction for using Prednisolone

We copied cited and copied the information on the leaflet from:
Medicine for children – information for parents and carers: prednisolone for asthma.
http://www.medicinesforchildren.org.uk/prednisolone-asthma

This leaflet has been written for parents and carers about how to use this medication in children. This information may differ from that provided by the pharmaceutical company, because their information is usually aimed at adult patients. Please read this leaflet carefully.

Name of drug

Lupred tablet contains of prednisolone.

When should I give prednisolone?

Prednisolone is usually given once each day, usually in the morning. Give the medicine at about the same time each day so that this becomes part of your child's daily routine, which will help you to remember.

How much should I give?

Your doctor will work out the amount (the dose) that is right for your child. It is important that you follow your doctor's instructions about how much to give.

How should I give it?

The pharmacist will prepare the prednisolone tablets by crushing the tablets, mixing it with the sweetener, and packing them in a daily paper-pack for your child.

You can mix it with a small amount of soft food such as yogurt, honey, or jam, or give a glass of milk or juice. Make sure your child swallows it straight away, without chewing.

When should the medicine start working?

Prednisolone usually takes 4–6 hours to have its full effect.

What if my child is sick (vomits)?

If your child is sick less than 30 minutes after having a dose of prednisolone, give them the same dose again.

If your child is sick more than 30 minutes after having a dose of prednisolone, you do not need to give them another dose. Wait until the next normal dose.

If your child is sick again, please contact us.

What if I forget to give it?

You can give your child the missed dose as soon as you remember on the same day. If you remember after they have gone to bed, do not give them the missed dose. Give the next dose in the morning as usual. Never give a double dose of prednisolone

What if I give too much?

It can be dangerous to give too much prednisolone. If you think you may have given your child too much prednisolone, contact us immediately.

Are there any possible side-effects?

We use medicines to make our children better, but sometimes they have other effects that we don't want (side-effects). It is unlikely that your child will have side-effects if they only take prednisolone for a few days. They are more likely to get side-effects if they are on a high dose, have extra doses or take prednisolone for a long time.

Side effects that you must do something about

- If your child has bad stomach pain or repeated vomiting (being sick), contact us straight away. This may be due to an ulcer or inflammation of the pancreas
- If your child develops a rash or severe/unexplained bruising, contact us straight away, as there may be a problem with your child's blood
- If your child has eye pain or changes in their vision, contact us straight away

Oral prednisolone for acute otitis media in children (OPAL) study

33

CHECK THE COMPLETION OF STUDY DOCUMENTS (by Appointed Nurse)

CONFIDENTIAL STUDY DOCUMENT BINDER

- FORM01. Study Recruitment Log Book
- CRF01. Consent Form
- CRF02. Study Registration Form
- CRF08. Randomisation Form

CASE REPORT FORM BINDER

- CRF03. Eligibility Form
- CRF04. Baseline Information Form
- CRF05. Outcome Form
- CRF10. Serious Adverse Event Reporting Form
- CRF11. Feedback Form
- FORM7. Guideline of Antibiotics for AOM
- FORM08. Prednisolone Dose for OPAL Study

COMPLETED AND NON-PARTICIPATING SUBJECT BINDER

- FORM05. Recapitulation of Completed Case Report Form
- FORM06. Recapitulation of Non-Participating Subject Form

Oral prednisolone for acute otitis media in children (OPAL) study

PREPARATION OF STUDY MEDICATION

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind, controlled study (OPAL Study)

Date _____

CRF07. Prescription for OPAL study medication

Prednisolone doses:

- Aged 6 months to < 2 years old = 10 mg per day
- Aged 2 years to < 6 years old = 20 mg per day
- Aged 6 years to 12 years old = 30 mg per day

Registration ID :
Name : _____
Age : _____ months / year(s) *[write and circle your answer]*
Study medication dose : _____ mg per day = _____ tablets per day

R/ OPAL study medication tablet .....
Sach lact add
m.f. pulveres dtd No. V
∫ 1 dd 1 pc (before 9 am)

(sign here)

DISPENSING THE STUDY MEDICATION

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine (CEEBM) Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral prednisolone for acute otitis media in children: a pilot pragmatic, randomised, open-label, single-blind, controlled study (OPAL Study)

Pharmacy ID : |__|__|__|__|__| Hospital ID : |__|__|__|

FORM03 – STUDY MEDICATION DISPENSING FORM (FOR PHARMACY)

Randomisation/ Registration ID	Date dispensed	Dose (mg/day)	Number of doses (day)	Initial dose (5 days) or additional dose

Lupred ® 5
Prednisolone 5 mg
TABLET

COMPOSITION
Each tablet contains:
Prednisolone 5 mg

PHARMACOLOGY
Prednisolone is a systemic corticosteroid with glucocorticoid and anti-inflammatory potencies. The mechanism of action of corticosteroids is thought to be by control of protein synthesis. Corticosteroids react with receptor proteins in the cytoplasm of sensitive cells in many tissues to form a steroid-receptor complex.

INDICATION
Allergic reaction, inflammation and other diseases that require glucocorticoid treatment, such as rheumatoid arthritis, collagen diseases, and dermatology disorders.

DOSAGE AND INSTRUCTION
Adults: 1 – 4 tablets per day or according to the doctor's instruction.
The dosage reduces gradually until reach the lowest effective dose.

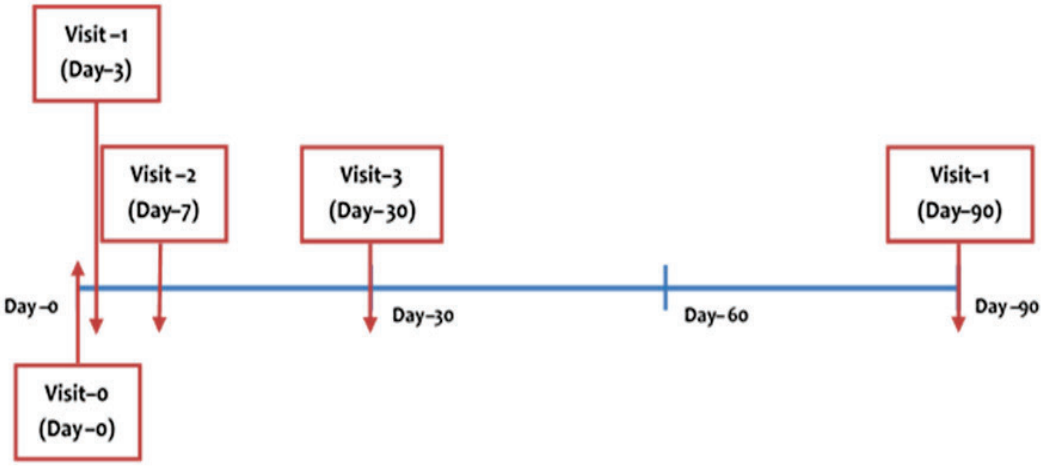
PRECAUTION
- Avoid the abrupt discontinuation in a long-term use
- Use with caution in paediatric patients who are still in the growing process
- Not recommended for pregnant and breast-feeding women
- Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses
- Risk of secondary adrenocortical insufficiency could be reduced by gradual reduction of dosage
- Use with caution in patients with diabetes mellitus because it can increase the gluconeogenesis and reduce the sensitivity to insulin
- Use with caution in patients with hypothyroidism because it can enhance the effect of corticosteroids
- Use with caution in patients with heart failure, infection diseases, chronic renal failure, and elderly

ADVERSE EFFECTS
- Water balance and electrolytes disturbance: Natrium retention, excretion of potassium, hypokalaemic alkalosis, hypertension, and congestive heart failure
- Musculoskeletal: Muscle weakness, steroid-induced myopathy, osteoporosis, vertebral compression fractures and pathologic fractures of long bones
- Gastrointestinal: Peptic ulceration with haemorrhage and perforation, pancreatitis, abdominal distension and ulcerative esophagitis
- Dermatological: Impaired wound healing, thinning of the skin, facial plethora, increased sweating
- Neurological: seizures, intracranial hypertension with papilloedema (cerebral pseudotumour), vertigo, headache

FAHRENHEIT
PT. PRATAPA NIRMALA
I001404-PG-1043

FOLLOW-UP VISITS

Follow-up timeline



Research team will send reminder text messages to remind the parents:

1. Give the study medication regularly to their children
2. Complete the Symptom Diary regularly
3. Come to the hospital for follow-up visits

INITIAL / BASELINE VISIT

Nurse
[Nurse station]

- Identification of paediatric patients with AOM symptoms who come to the clinic using **FORM01. Study recruitment log book**
- General examination (weight, height, temperature, blood pressure)
- Inform the appointed nurse or prepare the study binders
- Provide **CRF01. Information sheet and consent form** and **CRF02. Study registration form** to be read and completed while waiting for consultation

Physician
[Consultation room]

- Identify the eligibility to the study using **CRF03. Eligibility form**
- Provide information of the study and obtain the consent from the parents to the study using **CRF01. Information sheet and consent form**
- Stratify based AOM severity using **CRF03. Eligibility form**
- Data collection (interview for clinical history and ENT, otoscopic and tympanometry examination) using **CRF04. Baseline information form** and **CRF05. Outcome form**
- Inform and teach the parents in **completing CRF06. Symptom diary**
- Prescribe study medication using **CRF07. Prescription of study medication** and other medications

Appointed Nurse

- Conduct randomisation using **CRF08. Randomisation form** by accessing the randomisation system website or calling the randomisation call-centre
- Hand over **CRF07. Prescription of study medication** for those who were allocated to the prednisolone group
- Complete **CRF09. Follow-up visit card** by writing scheduled follow-up visit for the next three months
- Provide information of prednisolone use for those who were allocated to the prednisolone group and provide **FORM09. Instruction of prednisolone use for parents**
- Confirm that the ability of the parents in completing **CRF06. Symptom diary**
- Remind the parents to keep the information of intervention allocation confidential from the physician and audiologist
- Provide the transportation reimbursement and study souvenirs
- Compile and check the completion of all study documents, including **CRF02. Study registration form** and store them in the binders
- Secure the binders in a locked filing cabinet

Pharmacy

- Prepare and dispense the study medication, including the sweetener syrup
- Record the dispensing process using **FORM03. Study medication dispensing form**

Audiologist / Trained staff
[Tympanometry room/corner]

- Tympanometry examination and record the results on **CRF05. Outcome form**. The Physician then will interpret the result

Follow-up Visit

Nurse
[Nurse station]

- Identify the patients as a study subject in OPAL study
- Perform general examination
- Report this to the Appointed Nurse with the results of general examination

Appointed Nurse

- Prepare the study documents in Case report form binder and copy the general examination results to **CRF05. Outcome form**
- Identify side effects by interview and check **CRF06. Symptom diary**. These will be reported to the physician without acknowledging him about the intervention allocation, if possible
- Collect the **First mini-booklet of symptom diary** and check its completion and the adherence in taking the study medication, as well as check the left-over study medication
- Report this subject to physician

Physician
[Consultation room]

- Identify any complications, symptoms, side effects, conduct ENT and otoscopic examination
- Record the examination results on **CRF05. Outcome form** or **CRF10. Serious adverse events reporting form** for any serious side effects
- Interpret the tympanometry results

Audiologist
[Tympanometry room/corner]

- Tympanometry examination and record its results on **CRF05. Outcome form**

Appointed nurse

- Ask the Physician for prescription of study medication, if needed
- Complete **CRF09. Follow-up visit card** and remind the parents for the scheduled next visit
- Provide the transportation reimbursement and study souvenirs
- Compile and check the completion of all study documents and store them in the binders
- Secure the binders in a locked filing cabinet

THE PRINCIPLES OF GOOD CLINICAL PRACTICE

Good Clinical Practice (GCP) 40

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The principles of GCP (1) 41

1. Clinical trials should be conducted **in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).**

2. Before a trial is initiated, **foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society**. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. **The rights, safety, and well-being of the trial subjects are the most important considerations** and should prevail over interests of science and society.

4. **The available nonclinical and clinical information on an investigational product should be adequate** to support the proposed clinical trial.

5. Clinical trials should be **scientifically sound, and described in a clear, detailed protocol**.

6. A trial should be conducted **in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion**

The principle of GCP (2)

42

7. The medical care given to, and medical decisions made on behalf of, subjects should always be **the responsibility of a qualified physician** or, when appropriate, of a qualified dentist.
8. Each **individual involved in conducting a trial should be qualified by education, training, and experience** to perform his or her respective task(s).
9. **Freely given informed consent** should be obtained from every subject prior to clinical trial participation.
10. All **clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification**.
11. **The confidentiality of records that could identify subjects should be protected**, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. **Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP).** They should be used in accordance with the approved protocol.
13. **Systems with procedures that assure the quality of every aspect of the trial should be implemented**.

Essential terms in GCP (1)

43

Protocol	Randomisation	Blinding	Subject / Trial subject
Vulnerable subjects	Investigational product	Investigator	Sub-investigator
Informed consent	Impartial witness	Subject identification code	Case report form (CRF)
Investigator's brochure	Source documents	Source data	Adverse event (AE)

Adverse drug reaction (ADR)	Serious adverse drug reaction (serious ADR)	Unexpected adverse dug reaction

SETTING-UP THE STUDY SITES

44

Rooms and equipment for the study (1)

45

1) Nurse station

2) Consultation room

3) Audiology room/corner

4) Private room for randomisation

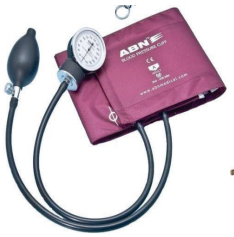
5) Pharmacy

Rooms and equipment for the study (2)

46

1) Weight scale
2) Measuring tape
3) Thermometer
4) Paediatric tensimeter
5) Headlamp or penlight
6) ENT tools
7) Tympanometry
8) Scanner/copy machine
9) Smart phone or PC with internet connection
10) Filing cabinet with lock










THE ASSESSMENT OF ADVERSE EFFECTS

47


Adverse Effects

48

CRF05 – OUTCOME FORM

14 Side effects

Does your child have these complaints after taking the medicine

14.1	Increased appetite	O Yes O No	14.8	Drowsiness	O Yes O No
14.2	Increased urine amount	O Yes O No	14.9	Anxiety/distractibility/mood swing	O Yes O No
14.3	Weight gain	O Yes O No	14.10	Headache	O Yes O No
14.4	Gastritis/abdominal pain	O Yes O No	14.11	Skin rash or diaper rash	O Yes O No
14.5	Nausea	O Yes O No	14.12	Candidiasis	O Yes O No
14.6	Vomiting	O Yes O No	14.13	Dry mouth / throat irritation	O Yes O No
14.7	Diarrhea	O Yes O No	14.14	Sleep disturbance	O Yes O No

Others: _____

Did you bring your child to doctor (clinic or outpatient)? O Yes O No
Reason: _____
Medicine prescribed: _____

Has your child has been admitted to hospital? O Yes O No
Reason: _____
Medicine prescribed: _____

Regarding the side effects, your action is/are (you may answer more than one):
- O Discontinuation of the study drug (prednisolone)
- O Continuation of the study drug
- O Discontinuation of other concomitant drugs as follows:
  1. _____ 3. _____
  2. _____ 4. _____

The treatment you prescribed for the management of side effects
1. _____; Dose _____; Frequency _____ / day
2. _____; Dose _____; Frequency _____ / day
3. _____; Dose _____; Frequency _____ / day
4. _____; Dose _____; Frequency _____ / day

Does this child require specific or additional tests or examination?
- O No
- O Yes. Please specify with the results:
  1. _____
  2. _____
  3. _____

REGISTRATION ID _____

CRF10. SERIOUS ADVERSE EVENTS REPORTING FORM

SUBJECT INFORMATION

Weight (kg) |___|___|,|___|___| kg

List any relevant tests, laboratory data, history, including pre-existing medical conditions _____

Any concomitant medication _____

ADVERSE EVENT

Report type ☐ Initial report ☐ Follow-up ☐ Final

Reason for reporting
☐ Requires or prolongs hospitalization ☐ Congenital anomaly
☐ Permanently disabling or incapacitating ☐ Life threatening
☐ Overdose ☐ Death
☐ Other (please specify) _____ Date of death _____ Cause of death _____

SUSPECTED DRUG

Name of suspected drug _____ Generic name _____
Dose details _____ Name of manufacturer _____
Date of occurrence |___|___|-|___|___|-|___|___|___|___| (date – month – year)
Duration of event |___|___| month(s) |___|___| day(s)
Starting date of medication |___|___|-|___|___|-|___|___|___|___| (date – month – year)
Route of administration _____ Indication _____
Discontinuation of drug because of event ☐ No ☐ Yes Dated (date / month / year): _____
If stopped/lowered dose, did the event resolve after this? ☐ Yes ☐ No ☐ N/A
If reintroduced did the event reappear? ☐ Yes ☐ No ☐ N/A

Outcomes	☐ Recovered	☐ Recovered with sequelae	☐ Continuing
	☐ Change in SAE	☐ Patient died	☐ Unknown
Severity	☐ Mild	☐ Moderate	☐ Severe
Action taken with study drug	☐ None	☐ Dose reduced	☐ Discontinued
	☐ Dose temporarily reduced	☐ Discontinued temporarily	
Other action*	☐ None	☐ Treated with medication	☐ Other

FEEDBACK

49

Feedback

Physicians

CRF11 – FEEDBACK FORM (for Physician only)

	Questions	Please place a checkmark (√) in the box corresponding to your answer
Information Sheet and Consent Form	How do you rate the process of providing patient information and informed consent to your patient?	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one	☐ It was too difficult to explain this to my patient/parent ☐ Time consuming ☐ There was too much information to explain ☐ I was not sure that my patient understood ☐ Others : _____
Otoscopic Examination	How do rate the process of conducting an otoscopic examination to your patient?	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one	☐ Patient was not cooperative ☐ The ear canal was too narrow ☐ Insufficient tool (e.g. the otoscope cylidner was too large) ☐ Ear wax and it was too difficult to extract ☐ The symptoms are definitely celar showing AOM ☐ Others : _____
Visual Analogue Scale (VAS)	How do you rate the process of providing related information and assisting your patient/parent to complete the visual analogue scale (VAS)?	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one	☐ It was too difficult to explain this to my patient/parent ☐ Time consuming ☐ I was not sure that my patient/parent understood ☐ My patient/parent seem not confidence with the answer ☐ Others : _____
Acute Otitis Media –	How do you rate the process of providing related information and assisting your patient/parent to complete the acute otitis	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult

Nurses

FEEDBACK FORM (for Nurses who conducts randomisation only)

	Questions	Please place a checkmark (√) in the box corresponding to your answer
Randomisation Process	How do you rate the randomisation process, in terms of obtaining the study ID and the allocation of the intervention (prednisolone group or control group)	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one.	☐ The CRF08. Randomisation form is too complicated ☐ The randomisation process was too confusing ☐ It was difficult to access the randomisation centre (randomi-sation website or by phone) to obtain the study ID and the allocation of the intervention ☐ It was difficult to explain to the patients that they were allocated to groups which reveice prednisolone or not ☐ Others _____
Dispensing the Study Medication Prescription	How do rate the process of dispensing the study medication prescription and keep the intervention allocation concealed from their Physician and Audiologists?	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one	☐ This process was too time consuming ☐ I encountered difficulties when I was providing relevant information on the intervention they received ☐ It was difficult to ask my patients/parents to keep the information of intervention allocation confidential ☐ Others: _____
The compilation and the Storage of Case report Forms	How do rate the process of the compilation and the storage of study documents and binders?	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one	☐ This process was too confusing ☐ This process was too time consuming ☐ It was difficult to find case report forms in the binder ☐ The checklist of case report forms was not helping ☐ Others: _____

Audiologists

FEEDBACK FORM (for Audiologist/Trained Staff only)

	Questions	Please place a checkmark (√) in the box corresponding to your answer
Tympanomtry Examination and the Competion of Tympanometry Section in the Case report Form	How do you rate the process of tympanometry examination and completing the tympanometry section in CRF?	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one.	☐ The patients' parents seem did not understand teh reason this examination being performed ☐ It was difficult to conduct this examination to my patients ☐ The 'Tympanometry section' in CRF05. Outcome form is confusing. The provided examination components are unfamiliar or different ☐ It was difficult to find the 'Tympanometry section' in the CRF05. Outcome form ☐ It was difficult to print out the copy of tympanometry result ☐ There were few components of this examination not provided in the form ☐ Others: _____

Feedback

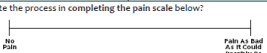
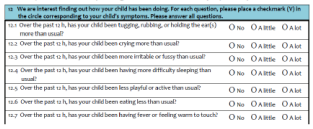
Pharmacists

FEEDBACK FORM (for Pharmacists only)

	Questions	Please place a checkmark (√) in the box corresponding to your answer
Preparation and Dispensing teh Study Medication	How do rate the preparation and dispensing process of the study medication?	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
	If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one.	☐ The instruction in CRF07. Prescription was confusing ☐ The preparation of the study medication was too time-consuming ☐ I encountered difficulties when providing the information about the study medication to my patients ☐ Others: _____

Parents

FEEDBACK FORM (for Parents only)

Questions	Please place a checkmark (√) in the box corresponding to your answer
How do you rate the process in **completing the pain scale** below? 	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
If your answer 'difficult' or 'very difficult', please place a checkmark (√) in the box corresponding to or write you reason(s). You may choose more than one.	☐ I did not understand how to compite this scale ☐ I need more information from my doctor ☐ The provided instruction in the form was unclear ☐ My doctor could not provide additional information that I need ☐ Others : _____
How do you rate the process in **completing the AOM-relevant symptom questionnaire** below? 	☐ Very easy ☐ Easy ☐ Neutral ☐ Difficult ☐ Very difficult
Apabila jawaban Anda 'Difficult' atau 'Very difficult', mohon berikan tanda centang di kotak yang sesuai atau berikan alasan Anda. Anda dipersilahkan untuk memilih lebih dari satu jawaban.	☐ It was difficult to understand the question(s) ☐ The options of answers were confusing ☐ The provided instruction in the form was unclear ☐ The question(s) was not suitable for my child, therefore I did not know how to answer the question(s): question no ____ ; ____ ; ____ ☐ I do not know how to complete the questionnaire

Thank you for your participation in the OPAL study.
Together, we will contribute in making Indonesian children' ears healthy!

APPENDICES – CHAPTER 5

Appendix 5.1. Diagnostic criteria for acute otitis media (AOM)

Appendix 5.2. Case report form CRF01. Information and consent form

Appendix 5.3. Case report form CRF02. Study registration form

Appendix 5.4. Case report form CRF03. Eligibility form

Appendix 5.5. Case report form CRF04. Baseline history form

Appendix 5.6. Case report form CRF05. Outcome form

Appendix 5.7. Case report form CRF06. Symptom diary

Appendix 5.8. Case report form CRF07. Prescription for OPAL study medication

Appendix 5.9. Case report form CRF08. Randomisation form

Appendix 5.10. Case report form CRF09. Follow-up reminder card

Appendix 5.11. Case report form CRF10. Adverse event assessment form

Appendix 5.12. Case report form CRF11. Serious adverse events reporting form

Appendix 5.13. Case report form FORM01. Study recruitment logbook

Appendix 5.14. Case report form FORM02. Study drug stock form

Appendix 5.15. Case report form FORM03. Drug dispensing form

Appendix 5.16. Case report form FORM04. Drug return form

Appendix 5.17. Case report form FORM05. Completed case report form

Appendix 5.18. Case report form FORM06. Antibiotics for acute otitis media

Appendix 5.19. Case report form FORM07. Study medication dose card

Appendix 5.20. Case report form FORM08. Instructions for using prednisolone

Appendix 5.21. Case report form FORM09. Information card

Appendix 5.22. Case report form FORM10. Lupred® information

Appendix 5.1. Diagnostic criteria for acute otitis media (AOM)

Mild AOM		**Severe AOM**	
Symptoms [1,2]	Mild ear pain Fever < 39°C Mildly ill (e.g. alert, responsive, well-response to antipyretics)	**Symptoms [1-3]**	Moderate to severe ear pain Fever ≥ 39°C Moderate or severely ill (e.g. vomiting, irritable, poor response to antipyretics)
Otoscopic Signs [4]	Mild hyperaemic TM Mild bulging	**Otoscopic signs [4]**	Moderate to severe hyperaemic TM Moderate to severe bulging, bulla formation, yellowish purulent appearance of TM TM perforation [5]
Other [1]	Children aged ≥ 2 years with bilateral AOM	**Other [1]**	Children aged < 2 years with bilateral AOM

TM: tympanic membrane

Reference:

1. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. Clinical practice guideline: the diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964–e99.
2. Le Saux N, Robinson JL, Canadian Paediatric Society Infectious Diseases and Immunization Committee. Management of acute otitis media in children six months of age and older. Paediatr Child Health. 2016;21(1):39-44.
3. Queensland Emergency Care Children Working Group. Acute otitis media – Emergency management in children. CHQ-GDL-60000 Version no 3.0. 26 September 2019. https://www.childrens.health.qld.gov.au/wp-content/uploads/PDF/guidelines/CHQ-GDL-60000-Acute-otitis-media.pdf

4. Kitamura K, Iino Y, Kamide Y, Kudo F, Nakayama T, Suzuki K, et al. Clinical Practice Guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan – 2013 update. Auris Nasus Larynx. 2015;42:99-106
5. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368:1429-1435.

Appendix 5.2. Case report form CRF01. Information and consent form

STUDY ID

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL Study)

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Oral prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL study)

[Steroids or anti-inflammatory drug for middle ear infection in children]

Invitation

You are invited to participate in a research study into the use of steroids (prednisolone) or an anti-inflammatory drug for middle ear infection in children. The study is being conducted by Dr. Respati W. Ranakusuma, an otorhinolaryngologists and a researcher at the Clinical Epidemiology and Evidence-Based Medicine (CEEBM) Unit Dr. Cipto Mangunkusumo Hospital–Faculty of Medicine Universitas Indonesia. It is part of an international collaborative study between CEEBM CMH-FMUI and the Institute for Evidence-Based Healthcare (IEBH), Bond University, Queensland, Australia.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. **What is the purpose of this study?**
   The purpose is to investigate the effect of steroids (prednisolone), as an alternative treatment, in children with acute or recent (less than 48 hours) middle ear infection in reducing: (1) ear pain and other symptoms related to middle ear infection; (2) the need of antibiotic treatment in children with mild symptom or shortening the duration of antibiotic use in children with severe symptom; (2) the risk of having complication (e.g. ruptured eardrum); and (3) the risk of having a new episode of middle ear infection in one and three months. To be able to assess the actual effect of the steroids, your child will receive either the steroid or the steroid dummy for five days. The dummy steroid will have similar taste, colour, and smell making it is not possible to differentiate with the real steroid.

2. **Why have my child and I been invited to participate in this study?**
   Your child and you have been invited because your child age between six months and 12 years and having symptoms/signs of acute middle ear infection (in 48 hours or less), such as ear pain, holding ear more frequently, more irritable. If visible, the ear examination using an otoscope will show red, yellowish, or bulging ear drum(s), or ear discharge. Otoscope is a tool consisted of a lamp, magnifying glass, and a silicone/plastic probe that will be inserted into the ear canal to identify the condition of the ear canal and ear drum. This examination is painless and generally takes 2 to 5 minutes. It may take longer if you child is uncooperative or have ear wax.

3. **What does participation in this study involve?**
   If you agree to participate in this study, your physician will ask you more questions regarding the history of your child's previous infection, allergy, vaccination, concurrent diseases, and the symptom severity in more detail, including your personal data and phone numbers to allow us contacting you if necessary. As only your child and you as the parent know the best of how severe the symptoms are, we will ask you to describe the pain severity and other symptoms using two pain measuring tools. The first tool is called Visual Analogue Scale (VAS). It is a 100-mm horizontal line, whereas the left end of the line represents 'no pain' and the right end represents 'the most painful'. We will ask you to draw a vertical line across this line at the point representing how bad the symptom that your child has been experiencing. The second tool is called Acute Otitis Media – the Severity of Symptoms scale (AOM-SOS)

which has seven questions. You will be asked to choose one of the severity scales ('no', 'a little', or 'a lot') that corresponds to your child's conditions. We will provide you a symptom diary that you have to complete every day for two weeks. This symptom diary is consisted of three booklet which listed two measuring tools, signs of complications, and medication taken each day. The will help us and your physician to assess your child improvement in daily basis. Your physician, nurse, or our research assistant will teach you how to complete the symptom diary.

We will ask you to come to the primary care centre or hospital at Day 3 and Day 7 following your first visit. During these visits, we will investigate whether the steroid will help reducing the ear pain and other relevant symptoms and whether it give unfavorable effects. We will also ask you to bring the symptom diary booklets, as well as the left-over and used paper wrap of study medication so we can ensure your child have taken the medication as ordered and have enough medication for five days. The nurse/research assistant will measure your child's weight, height, and temperature. The physician will examine your child ear, nose, and throat, and may order other tests (e.g tympanometry) if necessary. You then will meet the nurse/research assistant who will allocate your child to either receive the steroid (treatment group) or steroid dummy (placebo group). Your child has 50% chance for being allocated to receive the steroid and 50% chance to receive steroid dummy. We will do this process randomly, which will be conducted by the nurse/research assistant, where no one can predict or acknowledge in which group your child will be allocated to, as the results will be identified with codes. This process will require approximately 15 to 30 minutes. The nurse will copy the code in the prescription, which you will give away to the pharmacy at that primary care centre/hospital. The pharmacist will prepare the study medication by crushing the tablets, mixing it with sweeteners, and packing the study medication in a daily paper-package (you will receive five daily packages), and also provide a additional sweetener syrup which you can mix it with crushed tablet with a ratio of 3:1 to make the medication more palatable for your child. The nurse will give an instruction for taking the study medication. We strongly suggest you to give the study medication as a whole, every morning, once daily for five days. You can give this medicine with a glass of milk or juice, or with a small amount of soft food such as jam or yoghurt. The whole process will require 60 to 120 minutes depends on the cooperativity of your child.

At Day 14, we will visit your home to collect the symptom diary. We will contact you by phone at Day 30 (one month) and Day 90 (three months) to identify whether during these time, your child experiences a new episode of acute middle ear infection. To make this easy for you, our research personnel will send you a daily reminder text-message. If you agree to participate in this study, you will be asked to sign the Consent Form.

4. **What if I do not want to take part in this study, or if I want to withdraw later?**
Participation in this study is voluntary. It is completely up to you or both of you and your older child (aged 12 years), whether or not you participate. If you decide not to participate, it will not affect the treatment your child receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for your child. You may ask for consultation with another doctor, if you feel uncomfortable after deciding not to participate in the study. However, it may not be possible to withdraw your data from the study results if these have already had your identifying details removed.

5. **How is this study being paid for?**
The study is being for by Dr. Respati W. Ranakusuma, ORL which is supported by self-funded.

6. **Are there risks to my child in taking part in this study?**
   The foreseeable risks in taking part in this study are the bitter taste of study medication and potential side effects of prednisolone such as nausea, vomiting, abdominal pain, nervousness, mood swings, headache, increased blood sugar and weight gain, etc. Growth disorder could be one of the side effects however it usually occurs on the longer use of the steroids. We cannot predict whether your child will have one of these effects or not at all. The evidence from published studies, ensures us that the corticosteroids within the range of our dose and duration are safe and commonly used for children. You may feel that the whole process of this study will take longer time compared to usual doctor visit due to collection of information that will be conducted in this study. It may add some work for you to complete a symptom diary daily for the next 14 days. However, this is very important to be able to assess the day-by-day progress of your child condition.

7. **What happens if my child suffers injury or complications as a result of the study?**
   We will responsible of costs of consultation, test or examination, and treatment related to the side effects or complication from the use of study medication. We will monitor your child closely. You are also advised to contact our 24-hour call centre if you have any enquiries or questions regarding the study.

8. **Will I benefit from the study?**
   This study aims to further medical knowledge of future less-antibiotic-use treatment for acute middle ear infection, particularly in mild cases where usually antibiotics are being prescribed. This is very important since antibiotic use can increase the risk of side effects and antibiotic resistance. Antibiotic resistance is a condition where bacteria that making people sick, does not respond to antibiotic that aimed to kill them. This has been a health problem across the world due to its ability to increase the risk of having a worse or longer disease and causing death. However, this study may not directly benefit you.

9. **Will taking part in this study cost me anything, and will I be paid?**
   Participation in this study will not cost you anything, nor you will be paid. You will be reimbursed for reasonable travel expenses ($15) and we will provide souvenirs for your child. We will cover the registration and consultation fees for the additional two follow-up visits. We will provide the study medication and a sweetener syrup, but not for the other medications (e.g. antibiotics, flu/cough syrup) or additional tests or laboratory examination (e.g. tympanometry, x-ray, endoscopy examination) ordered by your physician.

10. **How will my confidentiality be protected?**
    Any identifiable information that is collected about your child in connection with this study will remain confidential, will be held securely, and will be disclosed only with your permission, or except as required by law. We will use your personal contact data (e.g. phone number, home address) to send a reminder text message, a home visit at Day-14, and to interview you by phone at one and three months.

11. **What happens with the results?**
    If you give us your permission by signing the consent document, we may report the study progress and result for monitoring and safety purposes, if necessary. We will also publish the study result in peer-reviewed journals or presentation at conferences or other professional forums. In any publication, information will be provided in such a way that you child cannot be identified.

12. What should I do if I want to discuss this study further before I decide?

When you have read this information, your physician or our research personal will discuss any queries you may have with you. If you would like to know more at any stage, please do not hesitate to contact Dr. Respati W. Ranakusuma, ORL by phone on +62 8111 012 185.

13. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by the Medical Ethics Committee FMUI and the Bond University's Human Research Ethics Committee (BUHREC) Bond University, Queensland, Australia. Any person with concerns or complaints about the conduct of this study should contact Dr. Respati W. Ranakusuma on +62 8111 012 185, or email OPAL.study@bond.edu.au.

The conduct of this study at Proklamasi ENT Hospital, Antam Medika Hospital, and several primare care centres in East and Central Jakarta, has been authorised by the the Health Agency for the Province of DKI Jakarta and the Directorate-General for Politics and General Government – The Ministry of Internal Affairs Republic Indonesia.

Thank you for taking the time to consider this study. If you wish to take part in, please sign the attached consent form.
This information sheet is for you to keep

CRF01. CONSENT FORM

Oral prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL study)

[Steroids or anti-inflammatory drug for middle ear infection in children]

1. I, _____
   of _____
   agree to participate in the study described in the participant information statement set attached to this form.
2. I acknowledge that I have read the participant information statement, which explains why my child has been selected, the aims of the study, and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.
3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm my child might suffer as a result of my child participation and I have received satisfactory answers.
4. I understand that my child can withdraw from the study at any time without prejudice to either my child and my relationship to my physician and the _____ Hospital.
5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.
6. I understand that I have any questions relating to my participation in this research, I may contact Dr. Respati W. Ranakusuma, ORL on telephone +62 8111 012 185, who will be happy to answer them.
7. I acknowledge receipt of a copy of this Consent Form and the Participation Information Statement.

Complaints may be directed to the OPAL Study Support Office at the Clinical Epidemiology and Evidence-Based Medicine Unit, Dr Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia, Building H Dr Cipto Mangunkusumo Hospital, Diponegoro 71, Jakarta 10430, Indonesia (phone +62 21 316 1760, email OPAL.study@bond.edu.au).

Signature of participant aged 12 years	**Name**	**Date**
_____	_____	_____
Signature of the parent	**Name**	**Date**
_____	_____	_____
Signature of witness	**Name**	**Date**
_____	_____	_____
Signature of researcher	**Name**	**Date**
_____	_____	_____

STUDY ID | |

REVOCATION OF CONSENT

Oral prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL study)

[Steroids or anti-inflammatory drug for middle ear infection in children]

I hereby wish to WITHDRAW my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with the _____ hospital or my medical attendants.

Signature of participant aged 12 years	**Name**	**Date**
_____	_____	_____
Signature of the parent	**Name**	**Date**
_____	_____	_____
Signature of witness	**Name**	**Date**
_____	_____	_____

The section for Revocation of Consent should be forwarded to Dr. Respati W. Ranakusuma, ORL at:

Clinical Epidemiology and Evidence-Based Medicine Unit
Dr Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia (CEEBM CMH-FMUI)
Dr Cipto Mangunkusumo Hospital Building H, 2nd floor
Jl Diponegoro 71, Jakarta 10430, Indonesia

Appendix 5.3. Case report form CRF02. Study registration form

Study ID ☐

CRF02. STUDY REGISTRATION FORM

PATIENT'S INFORMATION

Patient's name		Sex O Male O Female
Place and date of birth	_____ , _____	
Education	O None O Pre-school O Elementary school O Middle junior school O High school	
School attending hours	O once a week from: _____ am/pm to _____ pm/pm O Twice a week from: _____ am/pm to _____ pm/pm O three time a week from: _____ am/pm to _____ pm/pm O Four times a week from: _____ am/pm to _____ pm/pm O Daily (five times a week) from: _____ am/pm to _____ pm/pm O More than five times a week from: _____ am/pm to _____ pm/pm	
Day care	O Yes O No	
Day care hours	O once a week from: _____ am/pm to _____ pm/pm O Twice a week from: _____ am/pm to _____ pm/pm O three time a week from: _____ am/pm to _____ pm/pm O Four times a week from: _____ am/pm to _____ pm/pm O Daily (five times a week) from: _____ am/pm to _____ pm/pm O More than five times a week from: _____ am/pm to _____ pm/pm	
Home address		
Home telephone number		

Go to the next page for 'Parents' information'

Study ID | |

PARENTS' INFORMATION	
FATHER	
Father's name	
Place and date of birth	
Education	O None O Elementary school O Middle junior school O High school O Diploma/College O Bachelor O Masters O Doctoral
Occupation	O None O Government employee O Private employee O Entrepreneur O Others : _____
Home address	O Same with patient's address O Different address: _____ _____
Home telephone number	O Same with patient's telephone number O Different number: _____
Mobile number	
Email address	
MOTHER	
Mother's name	
Place and date of birth	
Education	O None O Elementary school O Middle junior school O High school O Diploma/College O Bachelor O Masters O Doctoral
Occupation	O Housewife O Government employee O Private employee O Entrepreneur O Others : _____
Home address	O Same with patient's address O Different address: _____ _____
Home telephone number	O Same with patient's telephone number O Different number: _____

Appendix 5.4. Case report form CRF03. Eligibility form

Date |__|__| – |__|__| – 201 |__|

Study ID

Doctor ID |__|__|__|

Site ID |__|__|__|

CRF03 – ELIGIBILITY FORM

INCLUSION CRITERIA	
OYes ONo	Definite or suspected acute otitis media with maximum onset of 48 hours Were you able to confirm otoscopically? OYes ONo
OYes ONo	Aged 6 months to 12 years
OYes ONo	Available for follow-up visits

EXCLUSION CRITERIA	
OYes ONo	Major medical conditions (e.g. heart/renal failure, DM)
OYes ONo	Immunocompromised (e.g. cancer treatment, HIV)
OYes ONo	Congenital malformation/syndromes (cleft palate)
OYes ONo	Ventilation tube(s)
OYes ONo	Exposed to persons with varicella/active Zoster infection in the past 3 weeks with no prior history of varicella infection or immunisation
OYes ONo	With high risk of strongyloidiasis infection
OYes ONo	Has taken oral/injection/topical steroids in the past 4 weeks
OYes ONo	Has taken oral antibiotics in the past 2 weeks
OYes ONo	Hypersensitive to prednisolone or other steroids

Is this child eligible for the trial?

All 'YES' at the inclusion criteria, AND
All 'NO' at the exclusion criteria
→ **Eligible, then INCLUDE**

At least one 'NO' at the inclusion criteria, OR
At least one 'YES' at the exclusion criteria
→ **Not eligible, then EXCLUDE**

Obtaining the CONSENT

→ NOT giving CONSENT → **EXCLUDE**

Giving CONSENT → **INCLUDE**

Do they have the following symptom(s)?

OYes ONo	Moderate to severe symptoms, locally or systemically (moderate to severe ear pain, fever ≥39°C, complications)
OYes ONo	Aged younger than 2 years with bilateral acute otitis media
OYes ONo	With perforation of tympanic membrane(s)
OYes ONo	If visible, otoscopic finding shows moderate to severe bulging and/or yellowish purulent tympanic membrane(s)

→ At least one 'YES' → **SEVERE AOM**

All 'NO' → **MILD AOM**

For each question, please tick (✓) your answer in the circle

Appendix 5.5. Case report form CRF04. Baseline history form

Study ID _____

CRF04 – BASELINE HISTORY FORM

1 Did (do) you breastfeed your child? O Yes O No

If you do, until the age of O ≤ 2 months O > 2 – 6 months O > 6 months

2 Have your child had an influenzae vaccine? O Yes O No O Do not know

If yes, how many times : _____

3 Have your child had a pneumococcus vaccine (PCV)? O Yes O No O Do not know

If YES, how many times : _____

4 How many episodes of acute respiratory infection (e.g. runny nose, cough, sore throat, fever) in the past 12 months?

O ≤ 3 episodes O > 3 episodes to 6 episodes O > 6 episodes

5 Did your child have a history of 3 or more episodes of ear infection (e.g. ear pain, ear discharge) in the past 12 months?

O Yes O No

If YES, the last episode was in: month _____ year _____

6 Is this the first time your child has ear infection? O Yes O No

If NOT, at what age did the first episode of ear infection start?

O ≤ 6 months O > 6 to 12 months O >12 to 24 months O > 2 to 5 years O > 5 years

7 Have your child had discharge from the ear? O Yes O No

If YES, on: O Right ear O Left ear The last time in: month _____ year _____

Has any doctor have confirmed that the ear drum is closed/healed? O Yes O No

The confirmation using otoscope O Yes O No O Not sure

8 Does your child have an allergy?

O Asthma

O Allergic rhinitis

O History of atopy in family

O None of the above. Others _____

9 Number of children (including the patient) who live in the house _____ children

10 Number of persons who smoke at home _____ person(s)

For each question, please tick (✓) your answer on the circle or write you answer on _____

Baseline History Form. Version 1.2. Date 8 July 2019

Appendix 5.6. Case report form CRF05. Outcome form

Study ID _____

CRF05 – OUTCOMES FORM

Baseline Visit (Day – 0) : |___|___| – |___|___| – 20 |___|___|

Complications (completed by physician)

1	Does your child experience discharge from the ear(s)?	O Yes	O No
2	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
3	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
4	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

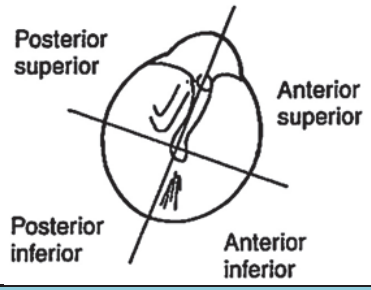
Physical examination (completed by physician)

5.1	**Weight** _____ kg	5.2 **Height** _____ cm			5.3 **Temp** _____ °C	
6	**Nose**	O Normal	O Oedema	O Hyperaemic	O Livid	O Discharge* serous / mucoid / mucopurulent
7	**Tonsils**	O Normal	O Hyperaemic	O Detritus	O Tonsil T1	O Tonsil T2 O Tonsil T3-4
8	**Pharynx**	O Normal	O Hyperaemic	O Oedema	O Granules	O Post nasal drip (PND)

Otoscopic examination (completed by physician)

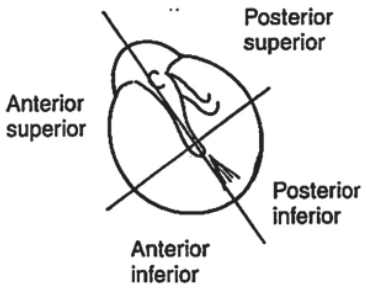
9.1 Right Ear (AD)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



9.2 Left Ear (AS)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



Other diagnostic tests (completed by physician)

10 Does this child require specific or additional tests or examination?

O No

O Yes. Please specify with the results:

O Naso/oto-endoscopy O Tympanometry O X-ray O Other : _____

Results:_____

_____

_____

11 Diagnosis (completed by physician)

O **Unilateral AOM – Right Ear (AOM AD)** O **Unilateral AOM – Left Ear (AOM AS)** O **Bilateral AOM (AOM ADS)**

12 Other diagnosis:

O Acute rhinitis O Acute rhinosinusitis O Acute tonsillitis/pharyngitis O Adenoiditis
O Allergic rhinitis O Chronic rhinosinusitis O Chronic tonsillitis/pharyngitis O Adenoid hypertrophy

For each question, please tick (✓) your answer on the circles or write you answer on _____

O Others: _____

13 Medicines that have been taken before the baseline visit (please circle your dose measurement)

1. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
2. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
3. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
4. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	

14 Medicines prescribed by you

Antibiotic	Dose : _____mg / Drops/ Teaspoon / Tablespoon Frequency : ____ times / day for _____ days

Other medicine

1. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
2. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
3. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
4. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
5. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day

Symptoms (for patient/parents)

15 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours?

16 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions

16.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
16.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
16.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
16.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
16.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
16.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
16.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Additional test / examination results (if available):

For each question, please tick (✓) your answer on the circles or write you answer on _____

Study ID |___|

Follow-up Visit-01 (Day-3) : |___|___| – |___|___| – 20 |___|___|

Complications (completed by physician)

1	Does your child experience discharge from the ear(s)?	O Yes	O No
2	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
3	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
4	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

Physical examination (completed by physician)

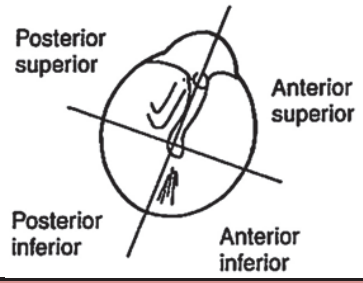
5.1 Weight _____ kg | **5.2 Height** _____ cm | **5.3 Temp.** _____ °C

6	**Nose**	O Normal	O Oedema	O Hyperaemic	O Livid	O Discharge* serous / mucoid / mucopurulent
7	**Tonsils**	O Normal	O Hyperaemic	O Detritus	O Tonsil T1	O Tonsil T2 O Tonsil T3-4
8	**Pharynx**	O Normal	O Hyperaemic	O Oedema	O Granules	O Post nasal drip (PND)

Otoscopic examination (completed by physician)

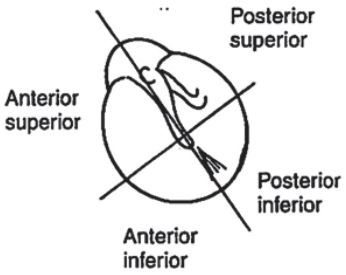
9.1 Right Ear (AD)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



9.2 Left Ear (AS)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



10 Medicines prescribed by you (please circle your dose measurement)

Antibiotic	Dose : _____mg / Drops/ Teaspoon / Tablespoon Frequency : ____ times / day for _____ days

Other medicine

1. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
2. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
3. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
4. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
5. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day

Symptoms (for patient/parents)

11 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours?

Study ID _____

12 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions

12.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
12.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
12.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
12.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
12.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
12.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
12.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

13 Side effects

Does your child have these complaints after taking the medicine

13.1 Increased appetite	O Yes	O No	13.8 Drowsiness	O Yes O No
13.2 Increased urine amount	O Yes	O No	13.9 Anxiety/distractibility/mood swing	O Yes O No
13.3 Weight gain	O Yes	O No	13.10 Headache	O Yes O No
13.4 Gastritis/abdominal pain	O Yes	O No	13.11 Skin rash or diaper rash	O Yes O No
13.5 Nausea	O Yes	O No	13.12 Candidiasis	O Yes O No
13.6 Vomiting	O Yes	O No	13.13 Dry mouth / throat irritation	O Yes O No
13.7 Diarrhea	O Yes	O No	13.14 Sleep disturbance	O Yes O No

Others: _____

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason: _____ Medicine prescribed: _____
Has your child has been admitted to clinic or hospital?	O Yes	O No	_____ Reason: Medicine prescribed: _____

Regarding the side effects, your action is/are (you may answer more than one):

O Discontinuation of the study medication

O Continuation of the study medication

O Discontinuation of other concomitant drugs as follows:

1. _____ 3. _____
2. _____ 4. _____

The treatment you prescribed for the management of side effects

1. _____; Dose _____; Frequency _____ / day
2. _____; Dose _____; Frequency _____ / day
3. _____; Dose _____; Frequency _____ / day
4. _____; Dose _____; Frequency _____ / day

Does this child require specific or additional tests or examination?	O No O Yes. Please specify with the results: O Naso/oto-endoscopy O Tympanometry O X-ray O Other : _____ Results:_____ _____ _____
Does this child require specific or additional treatment/medicine	O No O Yes. Please specify the treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day
Does this child require a hospitalisation?	O No O Yes. Please explain your reasons to hospitalise this child and the treatment will be given Reason: _____ _____ The treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day

Additional test /examination results (if available):

Study ID |___|___|___|___|

Follow-up Visit 02 (Day-7) : |___|___| – |___|___| – 20 |___|___|

Complications (completed by physician)

1	Does your child experience discharge from the ear(s)?	O Yes	O No
2	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
3	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
4	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

Physical examination (completed by physician)

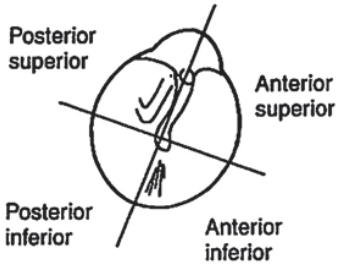
5.1 Weight _____ kg | **5.2 Height** _____ cm | **5.3 Temp** _____ °C

6	**Nose**	O Normal	O Oedema	O Hyperaemic	O Livid	O Discharge* serous / mucoid / mucopurulent
7	**Tonsils**	O Normal	O Hyperaemic	O Detritus	O Tonsil T1	O Tonsil T2 O Tonsil T3-4
8	**Pharynx**	O Normal	O Hyperaemic	O Oedema	O Granules	O Post nasal drip (PND)

Otoscopic examination (completed by physician)

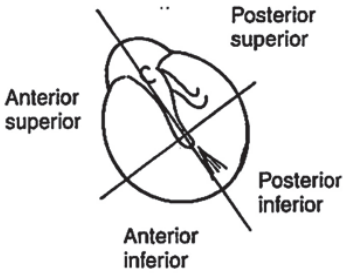
9.1 Right Ear (AD)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



9.2 Left Ear (AS)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



10 Medicines prescribed by you (please circle your dose measurement)

Antibiotic

Dose : _____mg / Drops/ Teaspoon / Tablespoon Frequency : ____ times / day for _____ days

Other medicine

1. _____ Dose : _____mg/ Drops / Teaspoon / Tablespoon Frequency : _____ / day
2. _____ Dose : _____mg/ Drops / Teaspoon / Tablespoon Frequency : _____ / day
3. _____ Dose : _____mg/ Drops / Teaspoon / Tablespoon Frequency : _____ / day
4. _____ Dose : _____mg/ Drops / Teaspoon / Tablespoon Frequency : _____ / day
5. _____ Dose : _____mg/ Drops / Teaspoon / Tablespoon Frequency : _____ / day

Symptoms (for patient/parents)

11 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours?

12 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions

12.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
12.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
12.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
12.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
12.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
12.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
12.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

13 Side effects

Does your child have these complaints after taking the medicine

13.1 Increased appetite	O Yes	O No	13.8 Drowsiness	O Yes	O No
13.2 Increased urine amount	O Yes	O No	13.9 Anxiety/distractibility/mood swing	O Yes	O No
13.3 Weight gain	O Yes	O No	13.10 Headache	O Yes	O No
13.4 Gastritis/abdominal pain	O Yes	O No	13.11 Skin rash or diaper rash	O Yes	O No
13.5 Nausea	O Yes	O No	13.12 Candidiasis	O Yes	O No
13.6 Vomiting	O Yes	O No	13.13 Dry mouth / throat irritation	O Yes	O No
13.7 Diarrhea	O Yes	O No	13.14 Sleep disturbance	O Yes	O No

Others: _____

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason: _____ Medicine prescribed: _____
Has your child has been admitted to clinic/hospital?	O Yes	O No	Reason: _____ Medicine prescribed: _____

Regarding the side effects, your action is/are (you may answer more than one):

O Discontinuation of the study medication

O Continuation of the study medication

O Discontinuation of other concomitant drugs as follows:

1. _____ 3. _____
2. _____ 4. _____

The treatment you prescribed for the management of side effects

1. _____; Dose _____; Frequency _____ / day
2. _____; Dose _____; Frequency _____ / day
3. _____; Dose _____; Frequency _____ / day
4. _____; Dose _____; Frequency _____ / day

Does this child require specific or additional tests or examination?	O No O Yes. Please specify with the results: O Naso/oto-endoscopy O Tympanometry O X-ray O Other : _____ Results:_____ _____ _____
Does this child require specific or additional treatment/medicine	O No O Yes. Please specify the treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day
Does this child require a hospitalisation?	O No O Yes. Please explain your reasons to hospitalise this child and the treatment will be given Reason: _____ _____ The treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day

Additional test /examination results (if available):

Study ID |___|

Follow-up 03 by Interview (Day-30) : |___|___| – |___|___| – 20 |___|___|

Recurrence

1 Within the past one month, does your child experience a new episode of ear pain	O Yes O No **When?** _____ days / weeks ago **How long?** _____ days / weeks **Did you bring your child to doctor** O Yes O No **The treatment:** 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day
2 Within the past one month, does your child experience common cold?	O Runny nose O Cough O Sore throat O Fever O Others: _____ **When?** _____ days / weeks ago **How long?** _____ days / weeks **Did you bring your child to doctor** O Yes O No **The treatment:** 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day

Symptoms

3	Does your child experience pain in the ear (s)? **If YES**, which ear O Right ear O Left ear	O Yes	O No
4	Does your child experience discharge from the ear(s)?	O Yes	O No
5	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
6	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
7	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

8 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions Otoscopic findings

8.1	Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little O A lot
8.2	Over the past 12 h, has your child been crying more than usual?	O No	O A little O A lot
8.3	Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little O A lot
8.4	Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little O A lot
8.5	Over the past 12 h, has your child been less playful or active than usual?	O No	O A little O A lot
8.6	Over the past 12 h, has your child been eating less than usual?	O No	O A little O A lot
8.7	Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little O A lot

For each question, please tick (✓) your answer on the circles or write you answer on _____

Study ID |___|

Follow-up 04 by Interview (Day-90) : |___|___| – |___|___| – 20 |___|___|

Recurrence

1 Within the past two months, does your child experience a new episode of ear pain	O Yes O No **When?** _____ days / weeks ago **How long?** _____ days / weeks **Did you bring your child to doctor** O Yes O No **The treatment:** 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day
2 Within the past two months, does your child experience common cold?	O Runny nose O Cough O Sore throat O Fever O Others: _____ **When?** _____ days / weeks ago **How long?** _____ days / weeks **Did you bring your child to doctor** O Yes O No **The treatment:** 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day

Symptoms

3	Does your child experience pain in the ear (s)? **If YES,** which ear O Right ear O Left ear	O Yes	O No
4	Does your child experience discharge from the ear(s)?	O Yes	O No
5	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
6	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
7	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

8 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions Otoscopic findings

8.1	Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
8.2	Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
8.3	Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
8.4	Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
8.5	Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
8.6	Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
8.7	Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

***** End *****

Study ID |___|

Additional visit : |___|___| – |___|___| – 20 |___|___|

Complications (completed by physician)

1	Does your child experience discharge from the ear(s)?	O Yes	O No
2	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
3	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
4	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

Physical examination (completed by physician)

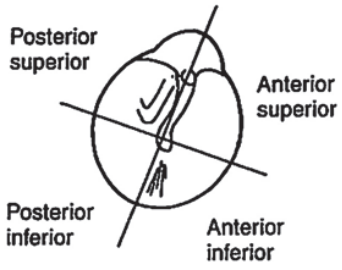
5.1 Weight _____ kg **5.2 Height** _____ cm **5.3 Temp** _____ °C

6	**Nose**	O Normal	O Oedema	O Hyperaemic	O Livid	O Discharge* serous / mucoid / mucopurulent
7	**Tonsils**	O Normal	O Hyperaemic	O Detritus	O Tonsil T1	O Tonsil T2 O Tonsil T3-4
8	**Pharynx**	O Normal	O Hyperaemic	O Oedema	O Granules	O Post nasal drip (PND)

Otoscopic examination (completed by physician) 9

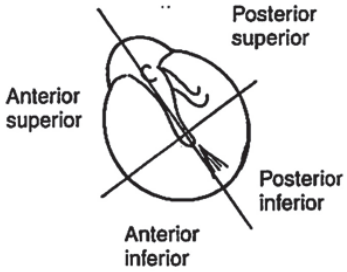
9.1 Right Ear (AD)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



9.2 Left Ear (AS)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



10 Medicines prescribed by you (please circle your dose measurement)

Antibiotic	Dose : _____mg / Drops/ Teaspoon / Tablespoon Frequency : ____ times / day for _____ days

Other medicine

1. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
2. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
3. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
4. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day
5. _____	Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day

Symptoms (for patient/parents)

11 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours?

12 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions

12.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
12.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
12.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
12.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
12.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
12.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
12.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

13 Side effects

Does your child have these complaints after taking the medicine

13.1 Increased appetite	O Yes	O No	13.8 Drowsiness	O Yes	O No
13.2 Increased urine amount	O Yes	O No	13.9 Anxiety/distractibility/mood swing	O Yes	O No
13.3 Weight gain	O Yes	O No	13.10 Headache	O Yes	O No
13.4 Gastritis/abdominal pain	O Yes	O No	13.11 Skin rash or diaper rash	O Yes	O No
13.5 Nausea	O Yes	O No	13.12 Candidiasis	O Yes	O No
13.6 Vomiting	O Yes	O No	13.13 Dry mouth / throat irritation	O Yes	O No
13.7 Diarrhea	O Yes	O No	13.14 Sleep disturbance	O Yes	O No

Others: _____

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason: _____ Medicine prescribed: _____
Has your child has been admitted to hospital?	O Yes	O No	Reason: _____ Medicine prescribed: _____

Regarding the side effects, your action is/are (you may answer more than one):

O Discontinuation of the trial drug (prednisolone)

O Continuation of the trial drug

O Discontinuation of other concomitant drugs as follows:

1. _____ 3. _____
2. _____ 4. _____

The treatment you prescribed for the management of side effects

1. _____; Dose _____; Frequency _____ / day
2. _____; Dose _____; Frequency _____ / day
3. _____; Dose _____; Frequency _____ / day
4. _____; Dose _____; Frequency _____ / day

Does this child require specific or additional tests or examination?	O No O Yes. Please specify with the results: O Naso/oto-endoscopy O Tympanometry O X-ray O Other : _____ Results:_____ _____ _____
Does this child require specific or additional treatment/medicine	O No O Yes. Please specify the treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day
Does this child require a hospitalisation?	O No O Yes. Please explain your reasons to hospitalise this child and the treatment will be given Reason: _____ _____ The treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day

Additional test /examination results (if available):

For each question, please tick (✓) your answer on the circles or write you answer on _____

Study ID |___|

Additional visit : |___|___| – |___|___| – 20 |___|___|

Complications (completed by physician)

1	Does your child experience discharge from the ear(s)?	O Yes	O No
2	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
3	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
4	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

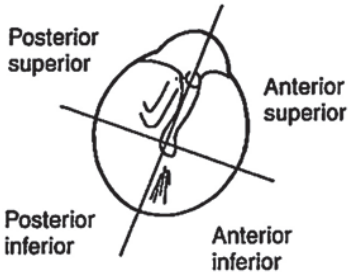
Physical examination (completed by physician)

5.1	**Weight** _____ **kg**	**5.2 Height** _____ **cm**			**5.3 Temp** _____ **°C**	
6	**Nose**	O Normal	O Oedema	O Hyperaemic	O Livid	O Discharge* serous / mucoid / mucopurulent
7	**Tonsils**	O Normal	O Hyperaemic	O Detritus	O Tonsil T1	O Tonsil T2 O Tonsil T3-4
8	**Pharynx**	O Normal	O Hyperaemic	O Oedema	O Granules	O Post nasal drip (PND)

Otoscopic examination (completed by physician)

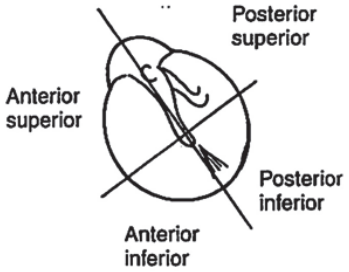
9.1 Right Ear (AD)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



9.2 Left Ear (AS)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



10 Medicines prescribed by you (please circle your dose measurement)

Antibiotic	Dose : _____mg / Drops/ Teaspoon / Tablespoon Frequency : ____ times / day for _____ days

Other medicine

1	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
2	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
3	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
4	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
5	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	

Symptoms (for patient/parents)

11 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours?

12 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions

12.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
12.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
12.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
12.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
12.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
12.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
12.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

13 Side effects

Does your child have these complaints after taking the medicine

13.1 Increased appetite	O Yes	O No	13.8 Drowsiness	O Yes	O No
13.2 Increased urine amount	O Yes	O No	13.9 Anxiety/distractibility/mood swing	O Yes	O No
13.3 Weight gain	O Yes	O No	13.10 Headache	O Yes	O No
13.4 Gastritis/abdominal pain	O Yes	O No	13.11 Skin rash or diaper rash	O Yes	O No
13.5 Nausea	O Yes	O No	13.12 Candidiasis	O Yes	O No
13.6 Vomiting	O Yes	O No	13.13 Dry mouth / throat irritation	O Yes	O No
13.7 Diarrhea	O Yes	O No	13.14 Sleep disturbance	O Yes	O No

Others: _____

Did you bring your child to doctor (clinic or outpatient)? O Yes O No
Reason: _____
Medicine prescribed: _____

Has your child has been admitted to hospital? O Yes O No
Reason: _____
Medicine prescribed: _____

Regarding the side effects, your action is/are (you may answer more than one):

O Discontinuation of the trial drug (prednisolone)

O Continuation of the trial drug

O Discontinuation of other concomitant drugs as follows:

1. _____ 3. _____
2. _____ 4. _____

The treatment you prescribed for the management of side effects

1. _____; Dose _____; Frequency _____ / day
2. _____; Dose _____; Frequency _____ / day
3. _____; Dose _____; Frequency _____ / day
4. _____; Dose _____; Frequency _____ / day

Does this child require specific or additional tests or examination?	O No O Yes. Please specify with the results: O Naso/oto-endoscopy O Tympanometry O X-ray O Other : _____ Results:_____ _____ _____
Does this child require specific or additional treatment/medicine	O No O Yes. Please specify the treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day
Does this child require a hospitalisation?	O No O Yes. Please explain your reasons to hospitalise this child and the treatment will be given Reason: _____ _____ The treatment: 1. _____; Dose _____; Frequency _____ / day 2. _____; Dose _____; Frequency _____ / day 3. _____; Dose _____; Frequency _____ / day 4. _____; Dose _____; Frequency _____ / day

Additional test /examination results (if available):

Study ID |___|

Additional visit : |___|___| – |___|___| – 20 |___|___|

Complications (completed by physician)

1	Does your child experience discharge from the ear(s)?	O Yes	O No
2	Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
3	Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)?	O Yes	O No
4	Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

Physical examination (completed by physician)

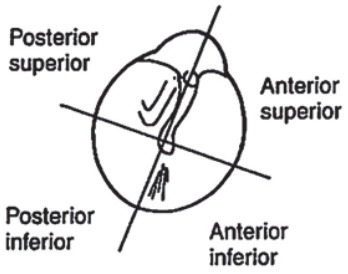
5.1 Weight _____ kg **5.2 Height** _____ cm **5.3 Temp** _____ °C

6	**Nose**	O Normal	O Oedema	O Hyperaemic	O Livid	O Discharge* serous / mucoid / mucopurulent
7	**Tonsils**	O Normal	O Hyperaemic	O Detritus	O Tonsil T1	O Tonsil T2 O Tonsil T3-4
8	**Pharynx**	O Normal	O Hyperaemic	O Oedema	O Granules	O Post nasal drip (PND)

Otoscopic examination (completed by physician)

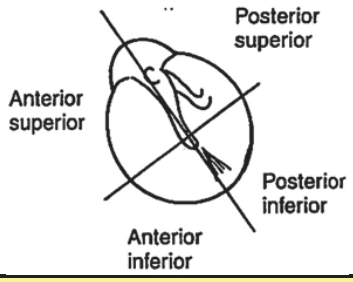
9.1 Right Ear (AD)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



9.2 Left Ear (AS)

O Normal O Cerumen O Hyperaemic
O Retraction O Air fluid level O Mild bulging
O Moderate/severe bulging O Complete effusion
O Opacification O Bulla
O Perforation O Dry O Discharge
O Serous O Mucoid O Mucopurulent



10 Medicines prescribed by you (please circle your dose measurement)

Antibiotic

Dose : _____mg / Drops/ Teaspoon / Tablespoon Frequency : ____ times / day for _____ days

Other medicine

1	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
2	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
3	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
4	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	
5	_____ Dose : _____mg/ Drops / Teaspoon / Tablespoon	Frequency : _____ / day	

Symptoms (for patient/parents)

11 Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 24 hours?

12 We are interest finding out how your child has been doing. For each question, please place a check mark in the circle corresponding to your child's symptoms. Please answer all questions

12.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
12.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
12.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
12.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
12.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
12.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
12.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

13 Side effects

Does your child have these complaints after taking the medicine

13.1 Increased appetite	O Yes	O No	13.8 Drowsiness	O Yes	O No
13.2 Increased urine amount	O Yes	O No	13.9 Anxiety/distractibility/mood swing	O Yes	O No
13.3 Weight gain	O Yes	O No	13.10 Headache	O Yes	O No
13.4 Gastritis/abdominal pain	O Yes	O No	13.11 Skin rash or diaper rash	O Yes	O No
13.5 Nausea	O Yes	O No	13.12 Candidiasis	O Yes	O No
13.6 Vomiting	O Yes	O No	13.13 Dry mouth / throat irritation	O Yes	O No
13.7 Diarrhea	O Yes	O No	13.14 Sleep disturbance	O Yes	O No

Others: _____

Did you bring your child to doctor (clinic or outpatient)? O Yes O No
Reason: _____
Medicine prescribed: _____

Has your child has been admitted to hospital? O Yes O No
Reason: _____
Medicine prescribed: _____

Regarding the side effects, your action is/are (you may answer more than one):

O Discontinuation of the trial drug (prednisolone)

O Continuation of the trial drug

O Discontinuation of other concomitant drugs as follows:

1 _____ 3. _____
2 _____ 4. _____

The treatment you prescribed for the management of side effects

1 _____; Dose _____; Frequency _____ / day
2 _____; Dose _____; Frequency _____ / day
3 _____; Dose _____; Frequency _____ / day
4 _____; Dose _____; Frequency _____ / day

Does this child require specific or additional tests or examination?

O No

O Yes. Please specify with the results:

O Naso/oto-endoscopy O Tympanometry O X-ray O Other : _____

Results:_____

_____
_____

Does this child require specific or additional treatment/medicine	O No O Yes. Please specify with the results: O Naso/oto-endoscopy O Tympanometry O X-ray O Other : _____ Results:_____ _____ _____
Does this child require a hospitalisation?	O No O Yes. Please explain your reasons to hospitalise this child and the treatment will be given Reason: _____ _____ The treatment: 1 _____; Dose _____; Frequency _____ / day 2 _____; Dose _____; Frequency _____ / day 3 _____; Dose _____; Frequency _____ / day 4 _____; Dose _____; Frequency _____ / day

Additional test /examination results (if available):

Appendix 5.7. Case report form CRF06. Symptom diary

DIARY-1 (Day-0 to Day-3)

Registration ID

Study ID | |

Hello Uncle / Aunty!!

My name is_____

I was born in_____

On date _____ month _____ year _____

If you find this Diary, I would be very grateful if you can return it to my Dad (mobile no. _____) or my Mom (mobile no. _____).

Study ID _____

Day-0 (*your first visit*) : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

Medicines given (please write the name, dose, and frequency)

Medicines have been given to your child before going to the hospital (from other doctor or chemist store)	_____	Dose : _____ mg / drop / teaspoon / tablespoon	Freq. : ____ /day	
	_____	Dose : _____ mg / drop / teaspoon / tablespoon	Freq. : ____ /day	
	_____	Dose : _____ mg / drop / teaspoon / tablespoon	Freq. : ____ /day	
	_____	Dose : _____ mg / drop / teaspoon / tablespoon	Freq. : ____ /day	
	_____	Dose : _____ mg / drop / teaspoon / tablespoon	Freq. : ____ /day	

Please list all medicines you give to your child today by marking the circle based on the frequency and the time

_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

For each question, please tick (✓) your answer on O or write you answer on _____

Thank you for filling the diary this morning.
Now please give your child the study medicine.

Notes:

Study ID |___|___|___|___|___|___|___|___|

Day – 1* : |___|___| – |___|___| – 20 |___|___|

*On the morning after your first visit to the hospital or doctor

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				
Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason:	_____	
			Medicine prescribed:	_____	

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Has your child has been admitted to hospital?	O Yes O No	Reason:	_____ _____
		Medicine prescribed:	_____ _____

Medicines given (please write the name, dose, and frequency)

Additional medicine from the chemist store or other (not precribed by your doctor)	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day

Please list all medicines you give to your child today by marking the circle based on the frequency and the time

_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Thank you for filling the diary this morning.
Now please give your child the study medicine.

Notes:

Study ID

Day-2 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

Medicines given (please write the name, dose, and frequency)

Medicines have been given to your child before going to the hospital (from other doctor or chemist store)	_____	Dose : _____ mg / body weight kg	Frequency : _____ / day
	_____	Dose : _____ mg / body weight kg	Frequency : _____ / day
	_____	Dose : _____ mg / body weight kg	Frequency : _____ / day
	_____	Dose : _____ mg / body weight kg	Frequency : _____ / day
	_____	Dose : _____ mg / body weight kg	Frequency : _____ / day

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No

For each question, please tick (✓) your answer on O or write you answer on _____

Others	_____		
Did you bring your child to doctor (clinic or outpatient)?	O Yes O No	Reason:	_____ _____
		Medicine prescribed:	_____ _____
Has your child has been admitted to hospital?	O Yes O No	Reason:	_____ _____
		Medicine prescribed:	_____ _____

Medicines given (please write the name, dose, and frequency)

Medicines have been given to your child before going to the hospital (from other doctor or chemist store)	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day

Please list all medicines you give to your child today by marking the circle based on the frequency and the time

_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Thank you for filling the diary this morning.
Now please give your child the study medicine

Notes:

Study ID

Day – 3 : |___|___| – |___|___| – 20 |___|___|
First visit to the primary care centre / hospital

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason: _____
			Medicine prescribed: _____
			Reason: _____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Has your child has been admitted to hospital?	O Yes O No	Medicine prescribed:	_____ _____

Medicines given (please write the name, dose, and frequency)

Additional medicine from the chemist store or other (not precribed by your doctor)	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day

Please list all medicines you give to your child today by marking the circle based on the frequency and the time

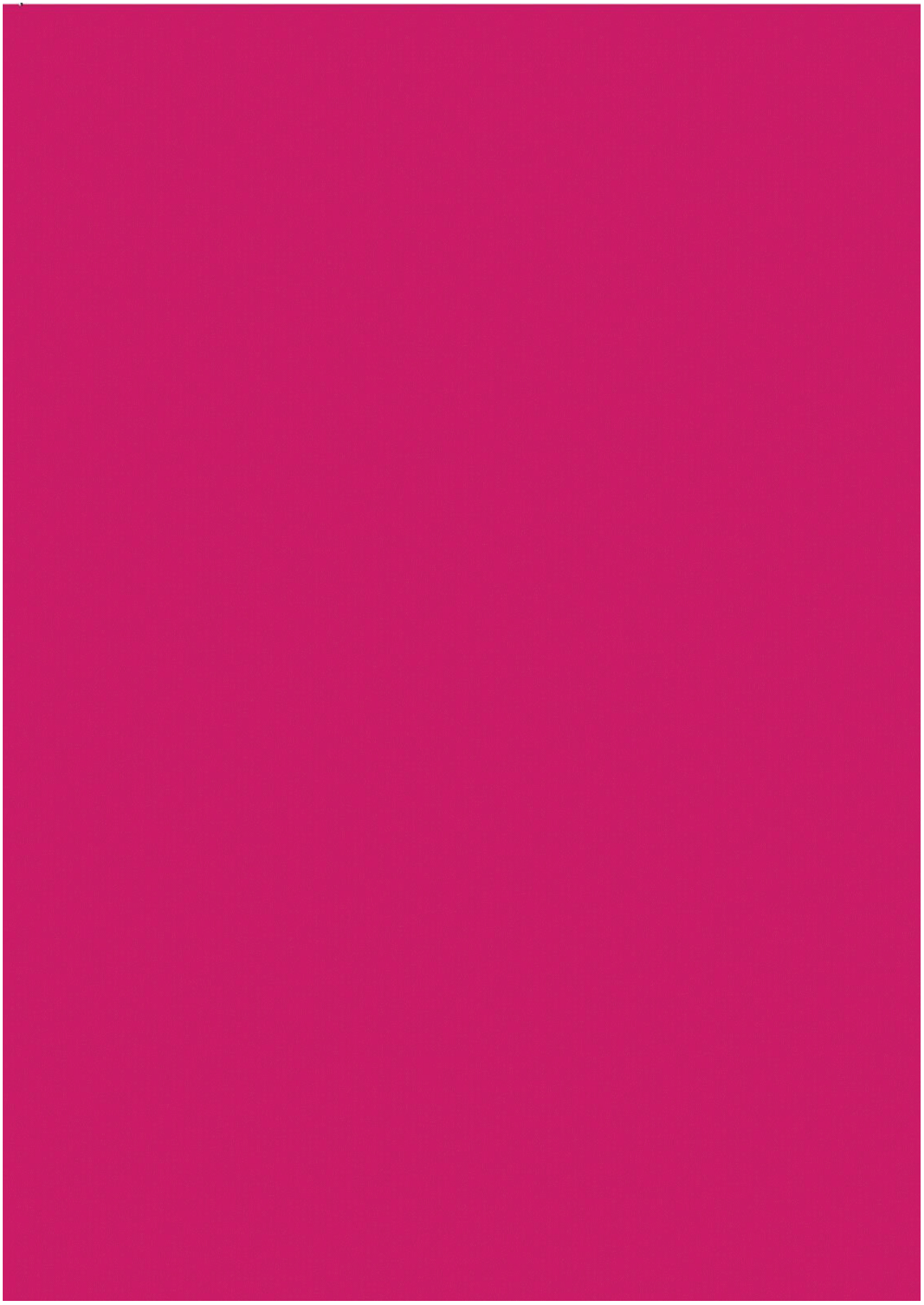
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Thank you for filling the diary this morning.
Now please give your child the study medicine.

Notes:

Thank you for completing the First Diary.

For each question, please tick (✓) your answer on O or write you answer on _____



DIARY – 2 (Day-4 to Day-7)

Registration ID

Study ID | |

Hello Uncle / Aunty!!

My name is_____

I was born in_____

On date _____ month _____ year _____

If you find this Diary, I would be very grateful if you can return it to my Dad (mobile no. _____) or my Mom (mobile no. _____).

Study ID

Day-4 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				
Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason:	_____	
			Medicine prescribed:	_____	
			Reason:	_____	

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Has your child has been admitted to hospital?	O Yes O No	Medicine prescribed:	_____ _____

Medicines given (please write the name, dose, and frequency)

Additional medicine from the chemist store or other (not precribed by your doctor)	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day

Please list all medicines you give to your child today by marking the circle based on the frequency and the time

_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Thank you for filling the diary this morning.
Now please give your child the study medicine.

Notes:

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Day – 5 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes O No
Others	_____			

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason:	_____
			Medicine prescribed:	_____
Has your child has been admitted to hospital?	O Yes	O No	Reason:	_____
			Medicine prescribed:	_____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Thank you for filling the diary this morning.
Now please give your child the study medicine.

Notes:

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID

Day-6 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason:	_____
			Medicine prescribed:	_____
Has your child has been admitted to hospital?	O Yes	O No	Reason:	_____
			Medicine prescribed:	_____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

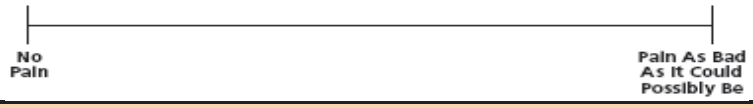
Notes:

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID

Day – 7 : |___|___| – |___|___| – 20 |___|___|
Second visit to the primary care centre / hospital

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)



2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes O No	Reason:	_____ _____
		Medicine prescribed:	_____ _____
		Reason:	_____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Has your child has been admitted to hospital?	O Yes O No	Medicine prescribed:	_____ _____

Medicines given (please write the name, dose, and frequency)

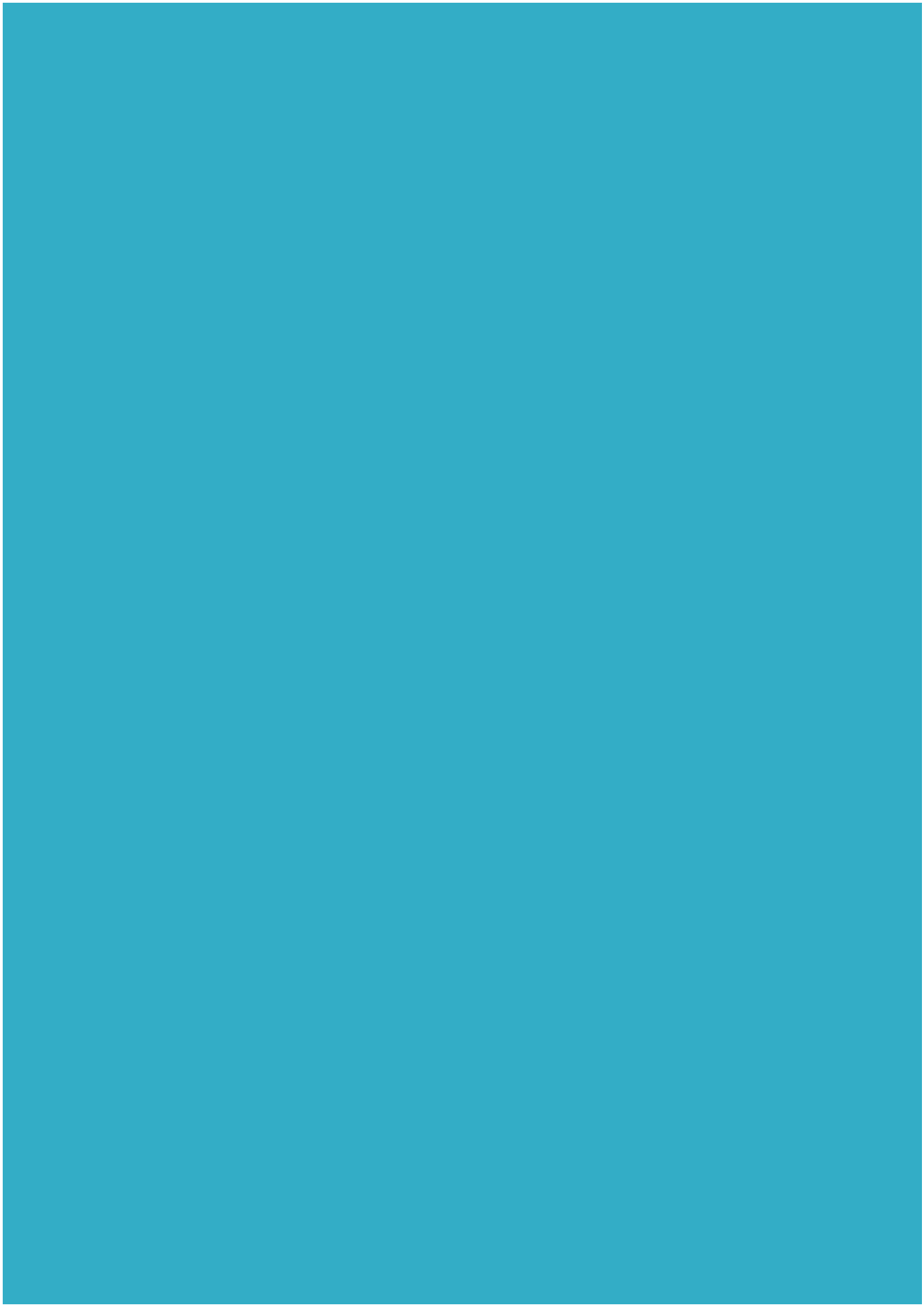
Additional medicine from the chemist store or other (not precribed by your doctor)	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day
	_____	Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day

Please list all medicines you give to your child today by marking the circle based on the frequency and the time

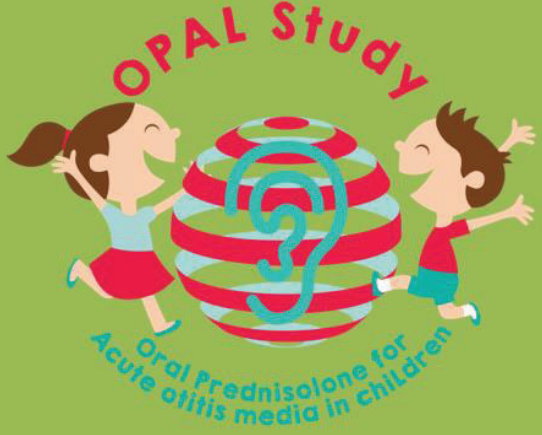
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

Thank you for completing the Second Diary.



DIARY–3 (Day-8 to Day-14)



Registration ID

Hello Uncle / Aunty!!

My name is_____

I was born in_____

On date _____ month _____ year _____

If you find this Diary, I would be very grateful if you can return it to my Dad (mobile no. _____) or my Mom (mobile no. _____).

Study ID _____

Day – 8 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes O No	Reason:	_____ _____
		Medicine prescribed:	_____ _____
Has your child has been admitted to hospital?	O Yes O No	Reason:	_____
		Medicine prescribed:	_____ _____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

Study ID _____

Day – 9 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes O No
Others	_____			

Did you bring your child to doctor (clinic or outpatient)?	O Yes O No	Reason:	_____ _____
		Medicine prescribed:	_____ _____
Has your child has been admitted to hospital?	O Yes O No	Reason:	_____
		Medicine prescribed:	_____ _____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Day – 10 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason: _____ _____
			Medicine prescribed: _____ _____
Has your child has been admitted to hospital?	O Yes	O No	Reason: _____
			Medicine prescribed: _____ _____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

For each question, please tick (✓) your answer on O *or write you answer on* _____

Study ID

Day – 11 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason:	_____ _____
			Medicine prescribed:	_____ _____
Has your child has been admitted to hospital?	O Yes	O No	Reason:	_____
			Medicine prescribed:	_____ _____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

Study ID |___|___|___|___|___|___|___|___|

Day – 12 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason: _____ _____
			Medicine prescribed: _____ _____
Has your child has been admitted to hospital?	O Yes	O No	Reason: _____
			Medicine prescribed: _____ _____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

Study ID _____

Day – 13 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes O No	Reason:	_____ _____
		Medicine prescribed:	_____ _____
Has your child has been admitted to hospital?	O Yes O No	Reason:	_____
		Medicine prescribed:	_____ _____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Day – 14 : |___|___| – |___|___| – 20 |___|___|

1. Please place a vertical line across the available horizontal line that best describes your or your child's pain during the past 12 hours? Please write the time accordingly ……. (am/ pm)

2. We are interest finding out how your child has been doing. For each question, please place a check mark in O corresponding to your child's symptoms. Please answer all questions. Please write the time accordingly ……. (am/ pm)

2.1 Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	O No	O A little	O A lot
2.2 Over the past 12 h, has your child been crying more than usual?	O No	O A little	O A lot
2.3 Over the past 12 h, has your child been more irritable or fussy than usual?	O No	O A little	O A lot
2.4 Over the past 12 h, has your child been having more difficulty sleeping than usual?	O No	O A little	O A lot
2.5 Over the past 12 h, has your child been less playful or active than usual?	O No	O A little	O A lot
2.6 Over the past 12 h, has your child been eating less than usual?	O No	O A little	O A lot
2.7 Over the past 12 h, has your child been having fever or feeling warm to touch?	O No	O A little	O A lot

Other symptoms

3 Does your child experience discharge from the ear(s)?	O Yes	O No
4 Does your child experience intense ear pain and pain behind the ear?	O Yes	O No
5 Does your child experience swelling/bulging, redness, tenderness, or dropping behind or of the ear(s)	O Yes	O No
6 Does your child experience facial asymmetry (e.g. when the child smiles, cries)?	O Yes	O No

7 Side effects

Does your child have these complaints after taking the medicine

7.1 Increased appetite	O Yes	O No	7.8 Drowsiness	O Yes	O No
7.2 Increased urine amount	O Yes	O No	7.9 Anxiety/distractibility/mood swing	O Yes	O No
7.3 Weight gain	O Yes	O No	7.10 Headache	O Yes	O No
7.4 Gastritis/abdominal pain	O Yes	O No	7.11 Skin rash or diaper rash	O Yes	O No
7.5 Nausea	O Yes	O No	7.12 Candidiasis	O Yes	O No
7.6 Vomiting	O Yes	O No	7.13 Dry mouth / throat irritation	O Yes	O No
7.7 Diarrhea	O Yes	O No	7.14 Sleep disturbance	O Yes	O No
Others	_____				

Did you bring your child to doctor (clinic or outpatient)?	O Yes	O No	Reason:	_____
			Medicine prescribed:	_____
Has your child has been admitted to hospital?	O Yes	O No	Reason:	_____
			Medicine prescribed:	_____

For each question, please tick (✓) your answer on O or write you answer on _____

Study ID _____

Medicines given (please write the name, dose, and frequency)					
Additional medicine from the chemist store or other (not precribed by your doctor)	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
	_____ Dose : _____ mg / drop / teaspoon / tablespoon Freq. : ____ /day				
Please list all medicines you give to your child today by marking the circle based on the frequency and the time					
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm
_____	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm	O ____ am/pm

Notes:

Thank you for completing the Last Diary.

Appendix 5.8. Case report form CRF07. Prescription for OPAL study medication

Date _____

CRF07. Prescription for OPAL study medication

Prednisolone doses:

- Aged 6 months to < 2 years old = 10 mg per day
- Aged 2 years to < 6 years old = 20 mg per day
- Aged 6 years to 12 years old = 30 mg per day

Randomisation ID : [ ]

Name : _____

Age : _____ months / year(s) *[write and circle your answer]*

Study medication dose : _____ mg per day = _____ tablets per day

R/ OPAL study medication tablet 5 mg ____ tab
Sach lact add
m.f. pulveres dtd No. V
ʃ 1 dd 1 pc (before 9 am)

R/ Sirplus sweetener syrup fl ____
ʃ 1 dd 1 pc (mix with study medication powder with ratio of 3:1)

Pharmacist's name:

Appendix 5.9. Case report form CRF08. Randomisation form

Study ID

Nurse ID : |___|___|___| **Site ID :** |___|___|___| **Date :** |___|___| – |___|___| – 201 |___|

CRF08 – RANDOMISATION FORM								
Eligibility criteria (cross-check with 'CRF01. Eligibility form' in the 'Case Report Form Binder' of this subject).								
All 'YES' for inclusion criteria?					**O Yes**		**O No**	
All 'NO' for exclusion criteria?					**O Yes**		**O No**	
Consent to participate in the study (cross-check with 'Form01. Informed consent' in the 'Case Report Form Binder' of this subject).								
Has the consent been obtained?					**O Yes**		**O No**	
RANDOMISATION								
Father's mobile phone no.								
Mother's mobile phone no.								
AOM Severity	**O Mild AOM**				**O Severe AOM**			
Date of Birth	**Date**		**Month**		**Year**		**Age**		**month/year***
RANDOMISATION RESULT								
Randomisation ID								
Name of personal who conducted randomisation		**Signature**		**Date of randomisation**				

Access to the MASCoT by clicking the link attached in the invitation email
https://mascot.org.au/collaborate/5d35f9b4-8ca8-41ce-b340-ae8ec9791abb
or
Contact 24-hour Call Centre +62 8111 012 185

Appendix 5.10. Case report form CRF09. Follow-up reminder card

Follow-Up Reminder Card

OPAL Study
Oral Prednisolone for Acute otitis media in children

Name	:	_____
Address	:	_____
		_____
Mobile No	:	_____

Clinical Epidemiology and Evidence-Based Medicine Unit (CEEBM)
Dr Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Institute for Evidence-Based Healthcare
Faculty of Health Sciences and Medicine, Bond University, Australia

Please bring this card to every follow-up visit

	Date of the Initial Visit	Scheduled Date of Follow-Up Visits	Actual Date of Follow-Up Visits	Note
Baseline / Initial Visit (Day 0)				
First Follow-Up Visit (Day 3)				
Second Follow-Up Visit (Day 7)				
Third Follow-Up Call (Day 30)				
Fourth Follow-Up Call (Day 90)				

Hospitals and Call Centre contact numbers

Proklamasi ENT Hospital
Jl. Proklamasi No.43
Operator : 021 390 0002, 021 392 4891 Ext. 0, 101, 227, 229
ENT Outpatient Clinic : Ext. 100, 236 244
Emergency Department : Ext. 235

Antam Medika Pulogadung Hospital
Jl. Raya Pemuda No. 1A
Operator : 021 806 14 888
ENT Outpatient Clinic : Ext. 1027
Paediatric Outpatient Clinic : Ext. 1019
Emergency Department : Ext. 1045

Kemayoran Primary Care Centre
Jl. Harapan Mulia Barat No. 1A
Operator : 021 425 1018, 021 428 01847

Pulo Gadung Primary Care Centre
Jl. Kayu Putih Selatan III No. 2B
Operator : 021 489 0519, 021 478 69633

24-Call Centre OPAL Study
Dr. Respati W. Ranakusuma, Sp.THT-KL : 08111 012 185

Appendix 5.11. Case report form CRF10. Adverse event assessment form

Study ID _____

CRF10. ADVERSE EVENT ASSESSMENT FORM

Assessor name _____ **Date** _____

The adverse event(s) is likely related to the study medication (prednisolone)

- ☐ Unrelated – clearly not related to prednisolone
- ☐ Unlikely – doubtfully related to prednisolone
- ☐ Possible – may be related to prednisolone
- ☐ Probable – likely related to prednisolone
- ☐ Definite – clearly related to prednisolone

Note: _____

_____

The adverse event(s) is likely related to other co-medication administered during the study

☐ Yes ☐ No

Medication name(s): _____

_____

Note: _____

_____

This adverse event(s) is considered as a serious adverse event

☐ Yes ☐ No

Note: _____

_____

Should this event be reported to the Ethics Committee?

☐ Yes ☐ No

Note: _____

_____

Conclusion: _____

_____

_____

Any recommendations for the ongoing study that arise from this event

1._____

2._____

3._____

4._____

For each question, please tick (✓) your answer in the box and fill ____

Adverse Event Assessment Form. Version 1.0. Date 8 July 2019

Appendix 5.12. Case report form CRF11. Serious adverse events reporting form

STUDY ID _____

CRF11. SERIOUS ADVERSE EVENTS REPORTING FORM

Weight (kg)	|____|____| , |____|____| kg		
Describe clinical history, pre-existing medical conditions, and any relevant tests or laboratory	_____ _____ _____ _____	Any concomitant medications	_____ _____ _____ _____

ADVERSE EVENT

Report type	☐ Initial report	☐ Follow-up	☐ Final
Reason for reporting	☐ Requires or prolongs hospitalization	☐ Congenital anomaly	
	☐ Permanently disabling or incapacitating	☐ Life threatening	
	☐ Overdose	☐ Death	
	☐ Other (please specify) _____	Date of death _____	
		Cause of death _____	

SUSPECTED DRUG

Name of suspected drug	_____	Generic name	_____
Dose details	_____	Name of manufacturer	_____
Date of occurrence	|____|____| - |____|____| - |____|____|____|____| (date – month – year)		
Duration of event	|____|____| month(s) |____|____| day(s)		
Starting date of medication	|____|____| - |____|____| - |____|____|____|____| (date – month – year)		
Route of administration	_____	Indication	_____
Discontinuation of drug because of event	☐ No	☐ Yes	Dated (date / month / year) : _____
If stopped/lowered dose, did the event resolve after this?	☐ Yes	☐ No	☐ N/A
If reintroduced did the event reappear?	☐ Yes	☐ No	☐ N/A
Outcomes	☐ Recovered	☐ Recovered with sequelae	☐ Continuing
	☐ Change in SAE	☐ Patient died	☐ Unknown
Severity	☐ Mild	☐ Moderate	☐ Severe
Action taken with study drug	☐ None	☐ Dose reduced	☐ Discontinued
	☐ Dose temporarily reduced	☐ Discontinued temporarily	
Other action*	☐ None	☐ Treated with medication	☐ Other
Withdrawn from the trial due to SAE	☐ No	☐ Yes	

REPORTER INFORMATION

Signature of reporter		Full name	
Date of signing	|____|____| - |____|____| - |____|____|____|____| (date – month – year)		

Appendix 5.13. Case report form FORM01. Study recruitment logbook

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL Study)

FORM01 – STUDY RECRUITMENT LOG BOOK

Study title :
Oral prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study

Hospital ID :

Study ID	Patient's name	Date screened	In the past 48 h, has your child been			Body weight (kg)	Body height (cm)	Body tempe-rature (°C)	Did patient go on the study? (YES or NO)	If YES, what is the Randomisation ID	If NO, please tell us reason not on the study below		
			experien-cing ear pain (YES or NO)	tugging/ rubbing her/his ear(s), been more fussy or crying more than usual? (YES or NO)	Experien-cing ear discharge ? (YES or NO)						Not eligible (YES or NO)	Did not give consent (YES or NO)	Was not approached (YES or NO). Write the reason

Please write 'Y' for 'YES' and 'N' for 'NO'.

Appendix 5.14. Case report form FORM02. Study drug stock form

Site ID : |___|___|___|

FORM02. STUDY DRUG STOCK FORM								
Date received	**Number of tablets**	**Name who received the drug**	**Signature**	**Date checked**	**Number of tablets**	**Name who checked the drug**	**Signature**	**Note**

Appendix 5.15. Case report form FORM03. Drug dispensing form

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL study)

Pharmacy ID : |___|___|___|___| **Site ID** : |___|___|___|

FORM03. DRUG DISPENSING FORM					
Randomisation ID	**Date Dispensed**	**Dose (mg/day)**	**Number of doses (days)**	**First dose or Additional ('F' or 'A')**	**Pharmacist's name**

Appendix 5.16. Case report form FORM04. Drug return form

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL Study)

Site ID : |___|___|___|

FORM04. DRUG RETURN FORM (FOR THE NURSE)				
Randomisation ID	**Date Returned**	**Number of left-over drug**	**Reasons for return**	**Nurse's name**

Appendix 5.17. Case report form FORM05. Completed case report form

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia

FORM05. COMPLETED CASE REPORT FORM	
Study title: Oral prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL study)	**Site ID :**

No	Randomisation ID	Enrolment date	Date of Visit-1 (Day-3)	Date of Visit-2 (Day-7)	Date of Interview-3 (Day-30)	Date of Interview-4 (Day-90)	Date of the completion of the study
			Please tick if patient completed these accordingly				

Appendix 5.18. Case report form FORM06. Antibiotics for acute otitis media

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL Study)

FORM06. ANTIBIOTICS FOR ACUTE OTITIS MEDIA

Initial immediate or delayed antibiotic therapy		Antibiotics after 48-72 hours of failure of initial antibiotic therapy	
Recommended first-line treatment	**Alternative treatment (if penicillin allergy)**	**Recommended first-line treatment**	**Alternative treatment**
Amoxicillin (80-90 mg/kg per day in 2 divided doses) OR Amoxicillin-clavulanate[a] (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day clavulanate (amoxicillin to clavulanate ration, 14:1) in 2 divided doses)	Cefdinir (14 mg/kg per day in 1 or 2 doses) Cefuroxime (30 mg/kg per day in 2 divided doses) Cefpodoxime (10 mg/kg per day in 2 divided doses) Ceftriaxone (50 mg IM or IV per day for 1 or 3 days)	Amoxicillin-clavulanate[a] (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day in 2 divided doses) OR Ceftriaxone (50 mg IM or IV per day for 3 days)	Ceftriaxone, 3 days Clindamycin (30-40 mg/kg per day in 3 divided doses), with or without third-generation cephalosporin (50 mg IM or IV per day for 3 days) Failure of second antibiotic Clindamycin (30-40 mg/kg per day in 3 divided doses) plus third-generation cephalosporin Tympanocentesis[b] Consult specialist[b]

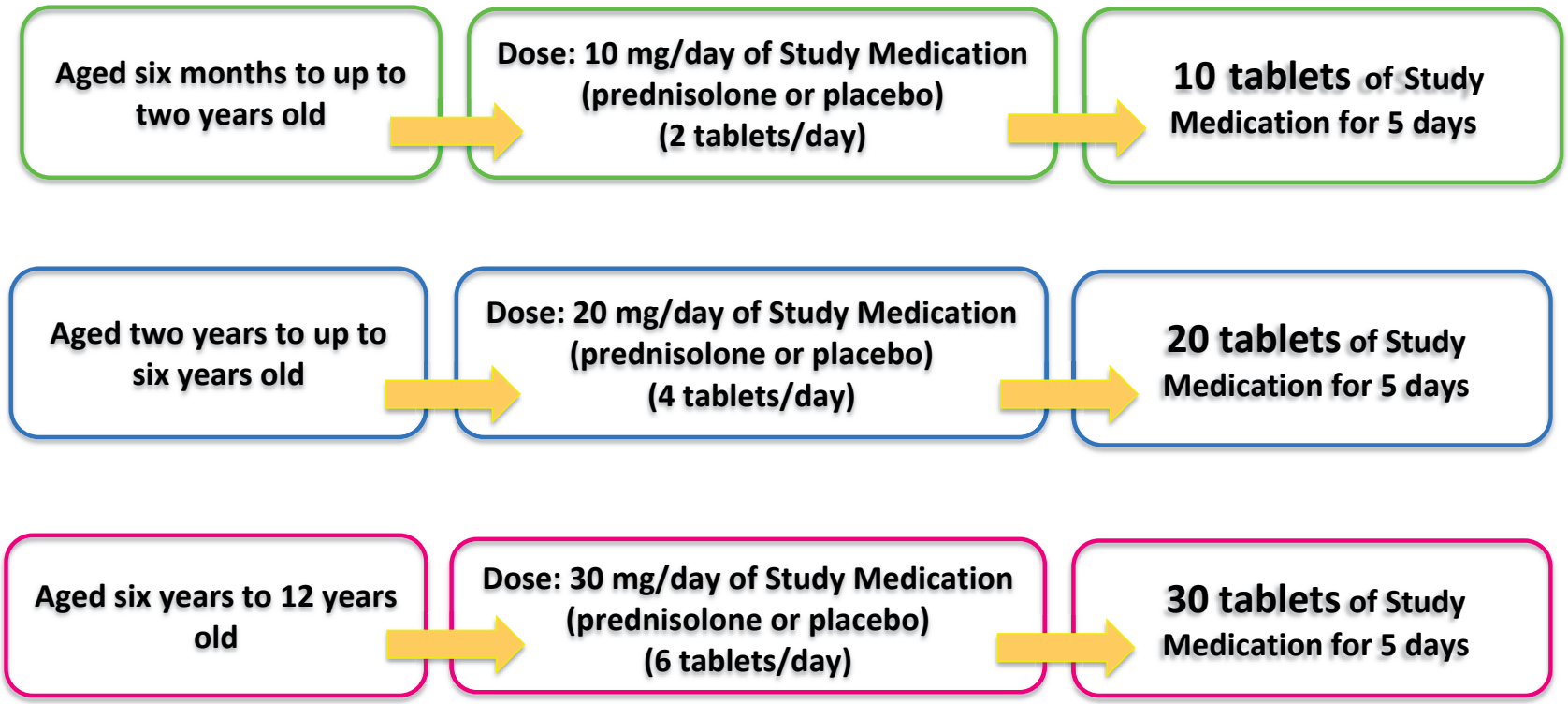
[a] *may be considered in patients who have received amoxicillin in the previous 3 o days or who have the otitis conjunctivitis syndrome;*
[b] *Perform tympanocentesis/drainage if skilled in the procedure, or seek a consultation from an otolaryngologist for tympanocentesis/drainage if the tympanocentesis reveals multidrug/resistant bacteria, seek an infection disease specialist consultation.*

Reference: Lieberthal AS, Carroll AE, Chonmaitree T, et al. Clinical Practice Guideline: The diagnosis and management of acute otitis media. The American Academy of Pediatrics. *Pediatrics.* 2013;131:e964-e99

Appendix 5.19. Case report form FORM07. Study medication dose card

dr. Respati W. Ranakusuma, SpTHT-KL
Clinical Epidemiology & Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine Universitas Indonesia
Oral Prednisolone for acute otitis media in children: a pragmatic, randomised, double-blind, placebo-controlled study (OPAL Study)

FORM07. STUDY MEDICATION DOSE CARD



Appendix 5.20. Case report form FORM08. Instruction for using Prednisolone

ORAL PREDNISOLONE FOR ACUTE OTITIS MEDIA IN CHILDREN (OPAL STUDY)

FORM08.Instruction for using Prednisolone

We copied cited and copied the information on the leaflet from:
Medicine for children – information for parents and carers: prednisolone for asthma. http://www.medicinesforchildren.org.uk/prednisolone-asthma

This leaflet has been written for parents and carers about how to use this medication in children. This information may differ from that provided by the pharmaceutical company, because their information is usually aimed at adult patients. Please read this leaflet carefully.

Name of drug

Lupred tablet contains of prednisolone.

When should I give prednisolone?

Prednisolone is usually given **once** each day, usually in the morning. Give the medicine at about the same time each day so that this becomes part of your child's daily routine, which will help you to remember.

How much should I give?

Your doctor will work out the amount (the dose) that is right for your child. It is important that you follow your doctor's instructions about how much to give.

How should I give it?

The pharmacist will prepare the prednisolone tablets by crushing the tablets, mixing it with the sweetener, and packing them in a daily paper-pack for your child.

You can mix it with a small amount of soft food such as yogurt, honey, or jam, or give a glass of milk or juice. Make sure your child swallows it straight away, without chewing.

When should the medicine start working?

Prednisolone usually takes 4–6 hours to have its full effect.

What if my child is sick (vomits)?

If your child is sick less than 30 minutes after having a dose of prednisolone, give them the same dose again.

If your child is sick more than 30 minutes after having a dose of prednisolone, you do not need to give them another dose. Wait until the next normal dose.

If your child is sick again, please contact us.

What if I forget to give it?

You can give your child the missed dose as soon as you remember on the same day. If you remember after they have gone to bed, do not give them the missed dose. Give the next dose in the morning as usual. Never give a double dose of prednisolone

What if I give too much?

It can be dangerous to give too much prednisolone. If you think you may have given your child too much prednisolone, contact us immediately.

Are there any possible side-effects?

We use medicines to make our children better, but sometimes they have other effects that we don't want (side-effects). It is unlikely that your child will have side-effects if they only take prednisolone for a few days. They are more likely to get side-effects if they are on a high dose, have extra doses or take prednisolone for a long time.

Side effects that you must do something about

- If your child has bad stomach pain or repeated vomiting (being sick), contact us straight away. This may be due to an ulcer or inflammation of the pancreas
- If your child develops a rash or severe/unexplained bruising, contact us straight away, as there may be a problem with your child's blood
- If your child has eye pain or changes in their vision, contact us straight away

Other side effects you need to know about

- child may have stomachache, feel sick or be sick (vomit) or may have indigestion (heartburn). Giving the medicine with some food may help
- Your child may have an increased appetite and may gain weight while taking prednisolone. You can help by making sure your child has plenty of physical activity, and by offering fruit and vegetables and low-calorie food, rather than food that is high in calories (e.g. cakes, biscuits, sweets)
- Your child may have trouble sleeping and nightmares and may feel depressed, or their behaviour may change in other ways. Contact us for advice if you are concerned

Side effects with high doses or long courses

- Prednisolone can slow growth and affect puberty. It can also cause growth of body hair and irregular periods in girls
- Your child may be more at risk of severe infections. They should stay away from anyone with an infection (such as chicken pox, shingles, measles) if they have not had these illnesses or have not been vaccinated for measles
- If your child is unwell and you are worried about an infection, contact us straight away
- Your child's skin may become thinner and heal more slowly than usual. Acne (spots) may become worse or your child may develop mouth ulcers or thrush (candidiasis). If you are concerned, contact us
- Your child may develop problems with their hip bones, or their bones may become weaker (osteoporosis). The muscles around the hips and shoulders may also become weaker. If your child has any difficulty walking or moving around, contact us
- Occasionally, prednisolone causes diabetes. If your child seems more thirsty than normal, needs to pass urine (wee) often, or starts wetting the bed at night, contact us

There may, sometimes, be other side-effects that are not listed. above. If you notice anything unusual and are concerned, please contact us.

Can other medicines be given at the same time?

You can give your child medicines that contain paracetamol or ibuprofen, unless your doctor has told you not to. Check with us or your doctor before giving any other medicines to your child. This includes herbal or complimentary medicines.

Is there anything else I need to know about prednisolone?

For children who have been taking prednisolone in high doses or for longer than 2-3 weeks

- They must not stop taking the medicine suddenly because they may get withdrawal symptoms: they will feel unwell, dizzy and thirsty and may be sick (vomit). If this occurs, you should contact us straight away
- If your doctor decides to stop prednisolone, they will reduce the dose gradually before stopping it completely. Make sure you follow your doctor's instructions
- Make sure that you always have enough medicine.

Where should I keep this medicine?

- Keep the medicine in a cupboard, away from heat and direct sunlight. It does not need to be kept in the fridge
- Make sure that children cannot see or reach it.
- Keep the medicine in the container it came in

WHO TO CONTACT FOR MORE INFORMATION

OPAL STUDY 24-HOUR CALL CENTRE

08111 012 185

Appendix 5.21. Case report form FORM09. Information card

INFORMATION CARD

Oral prednisolone for acute otitis media in children:
a pragmatic, randomised, double-blind, placebo-controlled study
(OPAL study)

Introduction

Acute otitis media (AOM) is an acute middle ear infection commonly found in children. High rate of antibiotic prescribing is evidence, although most AOM is non severe and will be improved under close observation and adequate pain management. Only one third of children with AOM having severe symptoms and signs, will benefit from antibiotics. Antibiotic use increases the risk of both unfavourable effects (e.g. vomiting, diarrhoea) and antibiotic resistance.

Due to potential harms of antibiotic use, alternative treatments for AOM that do not involve antibiotics is required. Current alternative treatments (i.e. decongestants, herbal products) demonstrate insufficient evidence of their benefits for AOM. Since AOM is mostly caused by the inflammation in the middle ear, thus corticosteroids as anti-inflammatory agents, could be potential treatment candidate for AOM. Although corticosteroids are effective for particular infection diseases, its effects for AOM remain uncertain. A large and high-quality clinical trial is required. Therefore, we are conducting a parallel, pragmatic, multicentre, randomised, double-blind, placebo-controlled trial.

Aim

To assess the effectiveness of oral corticosteroid as a monotherapy for children with mild AOM and as an addition to antibiotics for severe AOM.

Intervention

We randomly allocated children to receive either prednisolone or placebo. This is a double-blind study, thus physician, research team, or the parents will not acknowledge the intervention received by children.

Prednisolone and placebo given dose were based on age: 10 mg (6 month – 2 year), 20 mg (2–6 year), and 30 mg (6–12 year).

Physician may prescribe other medications if necessary. However, **we strongly advise NOT to prescribe oral corticosteroid** during this study, if possible. We also kindly ask you to provide a prescription copy to allow us to record other medication prescribe during the study.

Please do not hesitate to contact our principal investigator of this study for any enquires or questions:

Dr Respati W Ranakusuma, SpTHT-KL
08111 012 185
OPAL.study@bond.edu.AU

Appendix 5.22. Case report form FORM10. Lupred information

Lupred ® 5

Prednisolone 5 mg

TABLET

COMPOSITION

Each tablet contains:
Prednisolone 5 mg

PHARMACOLOGY

Prednisolone is a systemic corticosteroid with glucocorticoid and anti-inflammatory potencies. The mechanism of action of corticosteroids is thought to be by control of protein synthesis. Corticosteroids react with receptor proteins in the cytoplasm of sensitive cells in many tissues to form a steroid-receptor complex.

INDICATION

Allergic reaction, inflammation and other diseases that require glucocorticoid treatment, such as rheumatoid arthritis, collagen diseases, and dermatology disorders.

DOSAGE AND INSTRUCTION

Adults: 1 – 4 tablets per day or according to the doctor's instruction.
The dosage reduces gradually until reach the lowest effective dose.

PRECAUTION

- Avoid the abrupt discontinuation in a long-term use
- Use with caution in paediatric patients who are still in the growing process
- Not recommended for pregnant and breast-feeding women
- Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses
- Risk of secondary adrenocortical insufficiency could be reduced by gradual reduction of dosage
- Use with caution in patients with diabetes mellitus because it can increase the gluconeogenesis and reduce the sensitivity to insulin
- Use with caution in patients with hypothyroidism because it can enhance the effect of corticosteroids
- Use with caution in patients with heart failure, infection diseases, chronic renal failure, and elderly

ADVERSE EFFECTS

- Water balance and electrolytes disturbance: Natrium retention, excretion of potassium, hypokalaemic alkalosis, hypertension, and congestive heart failure
- Musculoskeletal: Muscle weakness, steroid-induced myopathy, osteoporosis, vertebral compression fractures and pathologic fractures of long bones
- Gastrointestinal: Peptic ulceration with haemorrhage and perforation, pancreatitis, abdominal distension and ulcerative esophagitis
- Dermatological: Impaired wound healing, thinning of the skin, facial plethora, increased sweating
- Neurological: seizures, intracranial hypertension with papilloedema (cerebral pseudotumour), vertigo, headache

FAHRENHEIT
PT. PRATAPA NIRMALA

I001404-PG-1043

- Endocrine: Disorders of menstruation, suppression of growth in children, secondary adrenocorticoid and non-responsive pituitary (particularly in stress, trauma, surgery or illness), metabolic effects, primarily involving the carbohydrates
- Ophthalmological: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and exophthalmos
- Metabolic: Nitrogen depletion due to protein catabolism
- Hypersensitivity: anaphylactic reaction

CONTRAINDICATION

- Patients who are known hypersensitivity to prednisone or prednisolone
- Peptic ulceration, active tuberculosis, osteoporosis, neurological disorders, renal and heart disorders
- Systemic fungal infections and ocular herpes simplex

INTERACTION WITH OTHER MEDICINES

- The use of aspirin and corticosteroid is not recommended in patients with non-specific ulcerative colitis
- Rifampicin, phenytoin, phenobarbital can increase the metabolism of corticosteroids
- Vaccination with live vaccine must be avoided

OVERDOSAGE

There is no specific antidot. Treatment is symptomatic with the dosage being reduced or the drug withdrawn.

STORAGE CONDITION

Store below 30°C.

DOCTOR's PRESCRIPTION IS A MUST

Manufactured by:
PT. PRATAPA NIRMALA
Tangerang – Indonesia